CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 28 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin (Also Called Abamectin) - 88-OR-06 - Section 18 Request to Use Avermectin on Pears in Oregon

Caswell No.: 63AB
Project No.: 8-0523
Record No.: 214047

FROM: William Dykstra, Reviewer
Toxicology Branch
Hazard Evaluation Division (TS-769C)

William Dykstra 3/28/88

TO: Don Stubbs, PM Team 41
Registration Support and
Emergency Response Branch
Registration Division (TS-767C)

THRU: Edwin R. Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Budd 3/28/88

The Oregon Department of Agriculture requests a FIFRA section 18 specific exemption for the use of avermectin to control spidermites on pears.

It is expected that 18,000 acres of pears may be treated. A maximum of 5624 gallons of product (884 lb ai, avermectin) will be needed. The formulation to be used is Agrimec 0.15 EC. Inerts are cleared under §180.1001.

No permanent tolerances have been established for avermectin. Temporary tolerances and experimental use permit (EUP) programs are currently in effect for citrus and cotton.

The label for section 18 for pears is correct with respect to signal word, precautionary labeling, and Statement of Practical Treatment.

The label was previously reviewed in a memorandum of April 23, 1987 from W. Dykstra to G. LaRocca (attached).

In the memorandum of April 23, 1987, the margins of safety (MOSs) for mixer/loader and sprayers (both with and without gloves) range from 350 to 1163 when maternolethality is the toxic endpoint and from 1399 to 4651 when cleft-palate (a developmental effect) is the toxic endpoint. Based on oral communication on March 17, 1988 with C. Lunchick of the Exposure Assessment Branch regarding expected exposure to workers in the section 18 use for pears, it was concluded that, if airblast spraying methods were used, the exposure to workers including pickers, in the section 18 use for pears would be comparable to the exposure to workers in the citrus EUP program. Therefore, the MOSs for workers in the section 18 use for pears are acceptable (greater than 100).

Pivotal toxicity data which were available in support of the temporary tolerances and EUP programs are listed below:

- Rat Acute Oral LD_{50}: 10.6 mg/kg (males); 11.3 mg/kg (females);
- Dermal Sensitization in Guinea Pig (Abamectin): negative for skin sensitization;
- 14-Week Oral Rat Study: NOEL $\geq$ 0.4 mg/kg/day (HDT);
- 18-Week Oral Dog Study: NOEL = 0.25 mg/kg/day;
- 1-Year Dog Study: NOEL = 0.25 mg/kg/day;
- Rat Teratology Study (Abamectin): negative for terata up to 1.6 mg/kg/day (HDT);
- Rabbit Teratology Study (Abamectin): negative for terata up to 2.0 mg/kg/day (HDT);
- Mouse Teratology Study (Abamectin): teratogenic LEL = 0.4 mg/kg/day (cleft-palate); teratogenic NOEL = 0.2 mg/kg/day;
- Mouse Teratology Study (delta-8,9-isomer): teratogenic LEL = 0.10 mg/kg/day (cleft-palate); teratogenic NOEL = 0.06 mg/kg/day;

- Mouse Maternotoxicity Study (Abamectin): LEL = 0.075 mg/kg/day (lethality); NOEL = 0.05 mg/kg/day;
- Mouse Maternotoxicity Study (delta-8,9-isomer): LEL = 0.50 mg/kg/day (lethality); NOEL = 0.10 mg/kg/day;
- Two-generation Rat Reproduction Study: NOEL = 0.12 mg/kg/day;
- Rat Metabolism Study;
- Ames Mutagenicity Assay (Abamectin): negative;
- Mutagenicity Assay for Chromosomal Aberration In Vitro in Chinese Hamster Ovary Cells: negative;
- Mammalian Cell Mutagenic Assay (Abamectin): negative for V-79 cells;
- Rat Hepatocyte Mutagenicity Study (Abamectin): under conditions of the study, abamectin (0.3 and 0.6 mM) caused an induction of single strand DNA breaks in rat hepatocytes in vitro; no effect was observed when the assay was carried out on hepatocytes from rats dosed in vivo at the LD_{50} dose level (10.6 mg/kg); and
- In Vivo Bone Marrow Mutagenicity Cytogenetic Study: negative in male mice at doses of 1.2 and 12.0 mg/kg.

Additionally, preliminary evaluation of a 94-week chronic toxicity/oncogenicity mouse study and a 2-year chronic toxicity/oncogenicity rat study did not reveal any potential oncogenic effects.

Toxicological studies with the delta-8,9-isomer and polar degradates of avermectin are required before permanent tolerances can be established (see Dykstra memorandum of April 23, 1987).

The provisional acceptable daily intake (PADI) is based on the NOEL of 0.12 mg/kg/day in the two-generation rat reproduction study. A thousandfold safety factor was used to calculate the PADI. At the LEL of 0.40 mg/kg/day in the study, effects included increased retinal folds in the weanlings, increase of dead pups, decreased viability indices, decreased lactation indices, and decreased pup body weight.

$$PADI = \frac{NOEL}{SF}$$

$$PADI = \frac{0.12 \text{ mg/kg/day}}{1000}$$

$$PADI = 0.00012 \text{ mg/kg/day}$$

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Based on the (attached) memorandum of March 11, 1988 from S. Stanton of the Residue Chemistry Branch (RCB) regarding avermectin on tomatoes, Tolerance Assessment System (TAS) analysis of dietary exposure yielded the following information:

	Published Temporary Tolerances	Section 18 (88-FL-05) Tomatoes	Total
U.S. Population	0.000039[a] (32.1%)[b]	0.000002 (2.05%)	0.000041 (34.2%)
Nonnursing Infants	0.000105 (87.8%)	0.000003 (1.9%)	0.000108 (89.7%)
Children, 1 to 6 yrs.	0.000093 (77.3%)	0.000004 (3.3%)	0.000097 (80.6%)

[a] Theoretical Maximum Residue Contribution in mg/kg/day.
[b] Exposure as percent of the PADI.

Additionally, the MOSs for developmental effects for the subgroup of females 13 years of age and older were estimated using the menu screen analysis. The following MOSs were calculated:

	Daily Exposure (mg/kg Body Wt)	MOS
Published Temporary Tolerances	0.00006	1000
Tomatoes (Pending Section 18)	0.00001	6000
All Uses (Published and Pending)	0.00007	860

A new TAS analysis and menu screen analysis will be provided by RCB for the section 18 on pears (oral communication on March 17, 1988 with S. Stanton of RCB).

The registrant of avermectin, Merck, has also provided a risk assessment for the section 18 for pears. Based on the registrant's risk assessment, the U.S. population will utilize 0.81 percent of the acceptable daily intake (ADI). Alternately, infants would be exposed to 2.78 percent of the ADI and children 1 to 6 to 1.83 percent of the ADI.

Additionally, the registrant calculates that the MOS for developmental effects and maternotoxicity will be 625 and 521, respectively, for the subgroup of females 13 years of age and older using the menu screen analysis.

Conclusions and Recommendations

If RCB can conclude that the percent PADI utilized is less than 100 percent and the MOS for development toxicity and maternolethality are greater than 100, the section 18 for pears can be toxicologically supported.

Attachments

Avermectin toxicology review

Page _____ is not included in this copy.

Pages 6 through 9 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

X A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

___ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005850

APR 23 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Abamectin (Avermectin) In/On Citrus - PP#7G3468/
7H5518; 50658-EUP-1 - Caswell No. 63AB -
Record No. 184274/184275 - Project No. 7-0140
Accession Nos. 265563 through 265577 and 265584

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: George LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

and

Exposure Assessment Branch
Hazard Evaluation Division (TS-769C)

THRU: Edwin Budd, Section Head
Review Section-II
Toxicology Branch
Hazard Evaluation Division (TS-769C)

and

Theodore M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Requested Action:

Review data in support of temporary tolerances and Experimental Use Permit (EUP) program for use on citrus.

Conclusions and Recommendations:

1. Toxicology Branch (TB) does not object to the EUP program and requested temporary tolerances.

   Margins of Safety (MOS), based on exposure data from Exposure Assessment Branch (EAB) for persons wearing long pants, long-sleeved shirts, gloves, and no gloves[1], and utilizing TB conclusions regarding dermal absorption in the monkey, yielded the following values.

Maternotoxicity	Abamectin (CF_1 Mouse) NOEL = 0.05 mg/kg/day	Endpoint is Lethality
Mixer/loaders (with gloves)	MOS	
50 Acres	1163	
100 Acres	581	
Sprayers (with gloves)	MOS	
50 Acres	1136	
100 Acres	568	
Sprayers (no gloves)[1]	MOS	
50 Acres	704	
100 Acres	350	

Teratogenicity	Abamectin (CF_1 Mouse) NOEL = 0.2 mg/kg/day	Endpoint is Cleft Palate
Mixer/loaders (with gloves)	MOS	
50 Acres	4651	
100 Acres	2326	
Sprayers (with gloves)	MOS	
50 Acres	4545	
100 Acres	2273	

[1] The proposed label requires mixer/loaders and sprayers to wear rubber gloves.

Teratogenic	Abamectin (CF_1 Mouse) NOEL = 0.2 mg/kg/day	Endpoint is Cleft Palate
Sprayers (no gloves)[1]	MOS	
50 Acres	2817	
100 Acres	1399	

[1] The proposed label requires mixer/loaders and sprayers to wear rubber gloves.

The MOS for harvesters (pickers) cannot be calculated at this time since the EAB review for dislodgeable residues has not yet been completed.

The precautionary labeling for the EUP program (copy attached) is required to include that users wear "protective clothing" (including long-sleeved shirt and pants) and rubber gloves when mixing and loading, and long-sleeved shirt and pants and rubber gloves during spraying. The precautionary labeling for pesticide respirator and goggles can be deleted from the label.

The human hazard signal word "Caution" should be added to the beginning of the precautionary statements.

2. The PADI for the temporary tolerances is based on the NOEL of 0.12 mg/kg/day in the two-generation rat reproduction study. At the LEL of 0.40 mg/kg/day in the study, effects included increased retinal folds in the weanlings, increase of dead pups at birth, decreased viability indices, decreased lactation indices, and decreased pup body weight. A 1000-fold safety factor has been utilized to calculate the PADI.

$$PADI = \frac{NOEL}{SF}$$

$$PADI = \frac{0.12 \text{ mg/kg/day}}{1000}$$

$$PADI = 0.00012 \text{ mg/kg/day}$$

Based on the most recent TAS analysis provided by RCB (memorandum of March 10, 1987 from D.S. Saunders to G. LaRocca), the proposed use on citrus would result in a TMRC for the U.S. population average of 0.000038 mg/kg/day, which would correspond to 32% of the PADI. The most highly

exposed subgroups would be nonnursing infants (0.000105 mg/kg/day, 88% of the PADI) and children 1 to 6 years of age (0.000092 mg/kg/day, 77% of the PADI).

It has been concluded that abamectin and the delta-8,9-isomer are teratogenic in the CF_1 mouse.

The TAS menu screen analysis determined that the highest predicted dietary exposure of females 13 years of age and older would be 0.00005 mg/kg/day.

The NOEL for maternotoxicity (lethality) used was 0.05 mg/kg/day (based on abamectin data).

The MOS for this end-point is as follows:

$$\text{MOS} = \frac{0.05 \text{ mg/kg/day}}{0.00005 \text{ mg/kg/day}}$$

$$\text{MOS} = 1000$$

The NOEL for terata (cleft palate) used was 0.06 mg/kg/day (based on the delta-8,9-isomer data).

The MOS for this end-point is as follows:

$$\text{MOS} = \frac{0.06 \text{ mg/kg/day}}{0.00005 \text{ mg/kg/day}}$$

$$\text{MOS} = 1200$$

3a. The delta-8,9-isomer of abamectin, which possesses abamectin-like toxicological activity, is a plant photodegradate that can range between 22 and 42 percent of the level of abamectin on citrus. Since the delta-8,9-isomer is a plant photodegradate, and does not occur in animal metabolism studies, the toxicity potential of this degradant has not been evaluated in the toxicological evaluation of abamectin or the animal drug, ivermectin. Therefore, to adequately characterize the toxic potential of the delta-8,9-isomer of abamectin, the following studies are required for permanent tolerances:

(1) Mutagenicity - Multitest Evidence

(2) Teratogenicity - Rat and Rabbit

(3) Two-Generation Reproduction Study - Rats

(4) 90-Day Feeding Study - Rats

For permanent tolerances, the following additional studies may be required:

(1) Oncogenicity - Mouse

(2) Chronic Toxicity/Oncogenicity - Rat

(3) 1-Year Dog Study

3b. "Polar Degradates" of Abamectin

The so-called "polar degradates" of abamectin, which apparently do not possess abamectin-like toxicological activity, constitute 54 to 84 percent of the total residue on citrus (based on radioactivity counts). The chemical structures of these "polar degradates" are unknown at this time. The following studies on "polar degradates" isolated from abamectin-treated citrus are required for permanent tolerances:

(1) NOEL for Maternotoxicity in CF_1 Mouse

(2) Teratogenicity - CF_1 Mouse

(3) Mutagenicity - Multitest Evidence

Based on the results of these studies, other data may be required for permanent tolerances.

4. TB has previously requested that EAB determine exposure to abamectin and the delta-8,9-isomer for persons exposed during harvesting of citrus. See memorandum of March 10, 1987.

5. TB has previously requested that EAB determine if ground water contamination will result from uses on citrus. See memorandum of March 10, 1987.

6. The submitted studies have been reviewed. Supplementary studies are required to be upgraded or repeated. Repeat or upgrading of studies reviewed in this report are required prior to establishment of permanent tolerances.

For the EUP and temporary tolerances, the existing data base is acceptable.

7. With respect to the deferral from RCB (memorandum of February 11, 1987 from L. Cheng) regarding the two 24-hydroxymethyl metabolites of avermectin B_1a and the delta-8,9-isomer of avermectin B_1a, TB will address this matter in a future memorandum.

005850

Review:

1. All the inerts in the formulation proposed for use (MK-936, 0.15 EC Miticide/Insecticide) are cleared for food use.

2. EUP Program

States, Acreages, and Quantity of Material for Proposed Experimental Use of Abamectin on Citrus in 1987

State	Acreage	Range Of Rates To Be Evaluated (lb/ai/A)	Maximum Number Application	Maximum Quantity Of Abamectin 0.15 EC Needed (gal)
California	1280	0.00625-0.025	3	640
Arizona	500	0.00626-0.025	3	250
Florida	1280	0.00625-0.025	3	640
Texas	200	0.00625-0.025	3	100
	Total 3260 Acres			1630 gal[1]/

3. Section F - Proposed Tolerances

Based on the residue data reported in this petition, where:

a. Three (3) treatments at 60-day intervals of up to 0.025 lb abamective/ai/A applied to citrus during the growing season, and

b. Citrus fruit harvested 7 days after the last treatment.

The petitioner requests amending 40 CFR Part 180 pursuant to Section 408(j) of the Federal Food, Drug, and Cosmetic Act by

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1/ For purpose of calculating the quantity of material needed, the maximum rate within the range (0.025 lb/ai/A) was used. A total of 1630 gal of abamectin 0.15 EC (244.5 lb/ai) is requested for use on a maximum of 3260 acres of citrus treated three times. This figure, therefore, represents an absolute maximum because it assumes that all acreage would be treated and the total acreage would receive three applications at the maximum rate.

Locations of Test Sites in Proposed Experimental Programs:

All citrus producing counties in the States of California, Arizona, Florida, and Texas are to be included.

proposing the following temporary tolerance of abamectin including its delta-8,9-iscmer:

Commodities	Tolerance
Citrus whole fruit	0.005 ppm
Cattle - meat, fat, and meat byproducts	0.01 ppm*
- milk	0.001 ppm

The petitioner also requests to amend 21 CFR pursuant to Section 409 of the Federal Food, Drug, and Cosmetic Act by proposing the following temporary tood/animal feed additive tolerances for the combined residues of abamectin and the delta-8,9-isomer:

Dried citrus pulp	0.10 ppm
Citrus oil	0.10 ppm

4. Section C - Toxicology

1. Section C1.b2

antitative Risk Assessment for Airblast Application : Abamectin for Citrus; September 4, 1986

Summary Prepared by Registrants

Calculations of the MOS utilize the lowest NOEL of abamectin technical of 0.05 mg/kg/day based on CF1 mouse by gavage in [redacted] and monkey dermal penetration of less than 1 percent. The registrants calculate the following MOS:

A. Unprotected whole body exposure.

(1) Mixer/loaders
MOS = 200 per 1 hr

(2) Sprayers
MOS = 83.25 per 8 hrs

B. Protected whole body exposure wearing long pants, long-sleeve shirts, impermeable gloves and personal hygiene.

*Recommended by RCB, memorandum dated February 11, 1987 from L. Cheng to G. LaRocca.

(1) Mixer/loaders
MOS = 8333 per 1 hr

(2) Sprayers
MOS = 1562 per 8 hrs

II. Volume II; Section C2; Position Document on the Toxicology of Abamectin and Proposed Acceptable Dietary Intake (ADI) (Accession No. 265564)

Registrant's Position on ADI

In the presentation of toxicology data, the registrant considers it reasonable to use the 1-year dog feeding study as the basis of the ADI. The NOEL for the study may be 0.25 mg/kg/day and the LEL may be 0.50 mg/kg/day with mydriasis as the effect. A one-hundredfold safety factor is used to calculate the ADI. The proposed ADI is therefore 0.0025 mg/kg/day.

TB Position on ADI

The ADI to be used by TB will be based on all of the assessed toxicity data of abamectin and the delta-8,9-isomer. A PADI is based on the NOEL of 0.12 mg/kg/day in the two-generation rat reproduction study. A 1000-fold safety factor is used for the PADI.

PADI = 0.00012 mg/kg/day

III. Attachment IVb

A. L-652, 280-OON (8,9-isomer of MK-0936); Acute Oral Toxicity Study in Mice (MSD; TT #84-112-0; April 9, 1986)

Test Material: Delta-8,9-isomer; 99% purity, Lot No. 03; delta-8,9-isomer of MK-936 is a photolytic degradation product.

Groups of 10 male and 10 female CF_1 mice, approximately 5 to 7 weeks old and weighing between 20 and 24 g were given 0, 5, 10, 20, 40, or 80 mg/kg of test material in [redacted] Observations were for 14 days. All animals were necropsied and brain, thoracic, and abdominal viscera were examined grossly.

Results: LD_{50} values for both male and female are greater than 80 mg/kg (3/10 and 1/10 deaths in males and females, respectively, at 80 mg/kg/day).

Toxic Signs: The signs of toxicity appeared generally within 60 to 90 minutes following compound administration and consisted of decreased activity, bradypnea, ataxia and ptosis. These signs were seen at all dose levels in males and all but the lowest dose level in females. In the second day, the same signs were seen in the 40 and 80 mg/kg males and the 80 mg/kg females. Death in male mice occurred in about 140 minutes to 4 1/2 hours, and in females about 2 1/4 hours to overnight.

Body Weight: Unaffected by treatment.

Necropsy: No compound-related gross lesions.

Classification: Guideline.

Toxicity Category II

B. A 8,9-Isomer of Avermectin B_1 (L-652, 280-OON); Oral Maternotoxicity and Teratology Studies (January 8, 1986)

(1) Oral Maternotoxicity Study in Mice (MSD; TT #84-722-0). Accession No. 265564

Test Material: 8,9-isomer of MK-0936; Lot No. 03; 99% purity.

The compound was given by gavage in sesame oil to groups of 7 to 11 mated 82-day-old female CF_1 mice (23.2 to 30.92 g) at doses of 1.5, 3.0, 6.25, 12.5, 25, and 50 mg/kg/day. A vehicle control group of 13 mated females was given 10 mL/kg of sesame oil. All mice were dosed on days 6 to 15 of gestation. The mice were observed daily and body weights were recorded on days 0, 6, 8, 10, 12, 14, 16, and 17 of gestation. Mice were killed on day 17 of gestation and the uterine contents were examined. Fetuses were weighed, sexed, and examined externally.

Results: There were treatment-related deaths at all dosage levels. There were 2 deaths each in the 3, 12.5, 25, and 50 mg/kg/day groups after 1 dose and 3 deaths in the 6.25 mg/ kg/day group after 1 dose. These groups were terminated on days 6 to 8 of gestation. There was 1 death in the 1.5 mg/kg/day group on day 8 of gestation after 2 doses. There were no other deaths and no abortions.

Some of the dead females (from the 1.5, 3.0, 12.5, and 25 mg/kg/day groups) were comatose/moribund a few hours prior to death. There were no other physical signs of toxicity. There was a slight but significant

decreases in body weight between days 16 and 17 of gestation in the 1.5 mg/kg/day group compared to the control which may have been related to treatment. There was no other evidence of maternotoxicity.

Treatment-related teratogenicity was seen at 1.5 mg/kg/day as an increased incidence of cleft palate (24 fetuses from 4 litters) compared to control (none). One female fetus (84-0325, 06) from a litter in which other fetuses had cleft palate, had exencephaly and omphalocele.

Conclusion: Maternotoxicity (including a treatment-related death) and teratogenicity were observed at the lowest dosage level tested (1.5 mg/kg/day). Groups dosed at dosage levels of 3 mg/kg/day and above were terminated, due to increased morality.

Classification: Minimum.

(2) A 8,9-Isomer of Avermectin B_1 (L-652, 280-00N); Volume II; Oral Maternotoxicity Study in Mice (MSD; TT #84-722-1; April 29, 1985). Accession No. 265564

Test Material: A 8,9-isomer of Avermectin B_1 (L-652, 280-OON); Lot No. 03; 99% purity.

Groups of 12 mated CF_1 mice received the test material by gavage at dosage levels of 0.05, 0.1, 0.5, and 1.0 mg/kg/day. An additional group of 12 mated females was given a 10 mL/kg volume of sesame oil and served as the control. At the beginning of the study, the females were approximately 10 weeks old and weighed 21.8 to 27.1 g. The test material was given orally by metal catheter once daily on days 6 through 15 of gestation. Body weights were recorded on days 0, 6, 8, 10, 12, 14, 15, and 17 of gestation.

All mice were examined grossly. On day 17 of gestation, pregnant females were killed and the uterine contents examined. Implants were counted and classified as resorptions, dead fetuses, or live fetuses. All fetuses were weighed, sexed, and examined externally. Statistical evaluation of the data was performed.

Results: There were single females in the 0.5 and 1.0 mg/kg/day groups which had clinical signs. One female given 0.5 mg/kg/day lost 6.9 g body weight between days 6 and 10 of gestation, had tremors following and prior to dosing on days 10 and 11 of gestation, and was killed in poor condition on day 11 of gestation. One female given 1.0 mg/kg/day lost 1.5 g in body weight between days

6 and 8 of gestation was lethargic on days 7, 8, and 9 of gestation, and was found dead on day 10 of gestation. There was no other evidence of maternotoxicity. The NOEL for maternotoxicity was 0.1 mg/kg/day.

There was a slight but nondose-related increase in the rate of resorption plus dead fetuses in all treated groups (12.7 to 16.7%) compared to the controls (9.6%). There was no effect on fetal weight. Teratogenicity was apparent at 1.0 mg/kg/day as an increased incidence of cleft palate (7 fetuses from 4 of 11 litters) compared to the control (none from 12 litters). There were slightly increased incidences of cleft palate at 0.1 and 0.5 mg/kg/day (13 fetuses from 2 litters, including 12 fetuses in 1 litter, and 1 fetus from 9 litters, respectively) compared to the control (none from 12 litters).

The occurrence of cleft palate at 0.1 mg/kg/day is considered treatment-related.

There were slightly increased incidences of exencephaly at 0.1 and 1.0 mg/kg/day (2 fetuses from 1 litter in each group) and a greater but nondose-related increase at 0.5 mg/kg/day (4 fetuses from 3 of 9 litters) compared to the control (1 fetus from 12 litters). Since there was no dose-response, the increased incidences of exencephaly at 0.1, 0.5, and 1.0 mg/kg/day are not considered treatmentrelated. Additionally, the historical control incidence of excencephaly showed 7 fetuses from 5 litters with this malformation in study TT #78-711-0. One fetus in the 1.0 mg/kg/day groups had a tail malformation and one fetus at 0.05 mg/kg/day had polydactyly. This malformation also occurred in one control fetus and therefore is not considered treatment-related.

Conclusion: The NOEL for maternotcxicity of the 8,9-isomer of Avermectin B_1 was 0.1 mg/kg/day. The apparent NOEL for teratogenicity and fetotoxicity was 0.05 mg/kg/day. Teratogencity was evidenced as cleft palate.

Classification: Minimum.

(3) 8,9-Isomer of Avermectin B_1 (L-652, 280-OON); Oral Teratogenicity Study in Mice (MSD; TT #85-710-0; June 4, 1985). Accession No. 265564

Test Material: 8,9-isomer of Avermectin B_1 (L-652, 280-OON); Lot No. 03; 99% purity.

Groups of 25 mated CF_1, female mice received the test material by gavage at dosage levels of 0.015, 0.03, and 0.06 mg/kg/day. An additional group of 25 mated females was given an equal volume of the sesame oil vehicle (10 mL/kg) and served as control. The test material was given orally by a metal catheter once daily on days 6 through 15 of gestation. At the beginning of the study, the females were approximately 10 weeks of age and weighed 19.2 to 28.7 g. Female body weights were recorded on days 1, 6, 8, 10, 12, 14, 16, and 17 of gestation.

On day 17 of gestation, the animals were sacrificed and the uterine contents examined. Implants were counted and classified as resorptions, dead fetuses or live fetuses. All fetuses were weighed, sexed, and examined externally and skeletally. Every third fetus in each litter and all fetuses with external malformations were examined viscerally including free-hand sections of fixed heads. All maternal animals were necropsied. Statistical analyses of the data were performed.

Results: There was no evidence of maternotoxicity. There were no deaths and no treatment-related abortions. There was one abortion in the 0.06 mg/kg/day group which was not considered treatment-related since abortions were not seen at higher dosages in other studies.

There were no effects on body weight or food consumption and no gross changes at necropsy.

There were no effects of treatment on fetal survival or fetal weight.

There were increased incidences of exencephaly in the 0.03 and 0.06 mg/kg/day groups (3 fetuses in both groups from 3 to 2 litters, respectively). This malformation is not considered compound-related since mice in previous studies of the 8,9-isomer of abamectin at higher dosages did not show a dose-related increase in exencephaly.

One fetus at the 0.015 mg/kg/day group had a cleft palate but is not considered compound-related since it was within the range of incidences observed in historical controls. Single litters in the 0.015 and 0.03 mg/kg/day groups had fetuses with hindlimb extension (4 and 1, respectively) which are not considered treatment-related since there was also a control fetus with hindlimb extension.

Visceral examination did not show any treatment-related fetal alterations. One fetus at 0.03 mg/kg/day had a ventricular septal defect which was not considered treatment-related since it was within the range

of historical controls. There were no compound-related effects with respect to fetotoxicity or teratogenicity based on skeletal examination. The low incidence of fetal malformations and delayed ossifications were not considered treatment-related, since they occurred in the controls and were comparable to those in the historical control.

Conclusion: The NOEL for developmental toxicity (teratogenicity and fetotoxicity) is 0.06 mg/kg/day (HDT). The MSDRL historical control incidences of selected fetal alterations in CF_1 mice provided by the registrant is shown below:

Table 12. 8,9-Isomer of Avermectin B_1 (L-652, 280-ONN): Oral Teratology Study in Mice. TT #85-710-0

Alteration	Fetuses Examined	Litters Examined	Fetuses with Alteration (%)	Litters with Alteration (%)
Exencephaly				
Overall	25,037	2,119	68 (0.27)	58 (2.7)
TT #78-711-0[a]	428	35	7 (1.64)	5 (14.3)
Cleft Palate				
Overall	25,037	2,119	69 (0.28)	63 (3.0)
TT #84-703-0[a]	235	21	3 (1.28)	3 (14.3)
Ventricular Septa Defect				
Overall	6,807	1,780	10 (0.15)	9 (0.51)
TT #74-710-0[a]	141	35	3 (2.13)	2 (5.7)
Diffuse Hemorrhagic Kidney				
Overall	6,807	1,780	13 (0.19)	13 (0.73)
TT #75-719-0[a]	127	34	3 (2.36)	3 (8.8)
Incomplete Oss. Skull Bone				
Overall	11,469	1,356	247 (2.15)	134 (9.9)
TT #76-723-0[a]	159	19	57 (35.1)	16 (84.2)
Thoracic Vertebra Malformation				
Overall	16,122	1,364	13 (0.08)	13 (0.95)
TT #70-709-0[a]	159	18	2 (1.26)	2 (11.1)
Missing Vertebra				
Overall	16,122	1,364	39 (0.24)	29 (2.1)
TT #77-711-0[a]	416	35	6 (1.44)	4 (11.4)

[a] Study with highest incidence of indicated alteration in our registrant's control data.

Table 12 (continued)

Alteration	Fetuses Examined	Litters Examined	Fetuses with Alteration (%)	Litters with Alteration (%)
Hypoplastic Rib				
Overall	16,122	1,364	11 (0.07)	9 (0.66)
TT #75-702-0[a]	433	38	3 (0.69)	2 (5.3)
~~TT #76-723-0[a]~~	~~459~~	~~49~~	~~51 (32.1)~~	~~16 (84.2)~~
Sternebral Malformation				
Overall	16,122	1,364	143 (0.89)	113 (8.3)
TT #75-701-0[a]	482	37	9 (1.87)	7 (18.9)
Incomplete Oss. Sternebra				
Overall	16,122	1,364	169 (1.05)	111 (8.1)
TT #75-707-0[a]	416	30	24 (5.77)	7 (23.3)
Incomplete Oss. Metacarpal				
Overall	16,122	1,364	3 (0.02)	2 (0.15)
TT #81-721-0[a]	224	19	1 (0.45)	1 (5.3)
Incomplete Oss. Metatarsal				
Overall	16,122	1,364	8 (0.05)	6 (0.44)
TT #78-711-0[a]	428	35	4 (0.94)	3 (8.6)

[a] Study with highest incidence of indicated alteration in our registrant's control data.

Classification: Minimum.

(4) 8,9-Isomer of Avermectin B_1 (L-652, 280-OON); Oral Teratogenicity Study in Mice (MSD; TT #85-710-1; September 16, 1985)

Test Material: 8,9-isomer of Avermectin B_1; Lot No. 03; 99% purity.

There were increased incidences of exencephaly at 0.03 and 0.06 mg/kg/day in MSD study TT #85-710-0.

Since previous studies of the 8,9-isomer of avermectin at higher doses did not show a dose-related increase in exencephaly, the present additional study (TT #85-710-1) was conducted at similar and higher dosages to confirm that the 8,9-isomer does not cause exencephaly in this dosage range.

Groups of 25 mated female CF_1 mice received dosages of the test material at levels of 0.015, 0.03, 0.1, and 0.5 mg/kg/day. An additional group of 25 mated females was given an equal volume of 10 mL/kg sesame oil and served as the control. The test material and vehicle was given orally by metal catheter once daily on days 6 through 15 of gestation. At the beginning of the study, the females were approximately 9 to 10 weeks of age and weighed 21.5 to 28.5 g. Female body weights were recorded on days 0, 6, 8, 10, 12, 14, 16, and 17 of gestation.

On day 17 of gestation the animals were sacrificed and the uterine contents examined. Implants were counted and classified as resorptions, dead fetuses, or live fetuses.

All fetuses were weighed, sexed, and examined externally and skeletally. Every third fetus in each litter and all fetuses with external malformations were examined viscerally including free-hand sections of Bouin's fixed heads. All maternal animals were necropsied. Statistical analyses of the data were performed.

Results: There was 1 treatment-related death in the 0.5 mg/kg/day group after 6 doses on day 12 of gestation. This female was lethargic and had bilateral chromodarcryorrhea beginning on day 9 of gestation and continuing until moribund sacrifice. This female consumed no food between days 9 and 11 of gestation and lost a total of 6.3 g in body weight. There were no additional effects in maternal body weight gain and food consumption. There was no effect on fetal survival and fetal body weight. There was a significant increase in the incidence of dead and resorbed fetuses at 0.03 mg/kg/day (16.3% vs. 9.0% in control). These findings are not considered compound-related since they were not dose-related.

Teratogenicity was observed at 0.5 mg/kg/day as cleft palate (24 fetuses from 6 litters) compared to control (none). There were also 6 fetuses from 1 litter at 0.1 mg/kg/day with cleft palate which are considered treatment-related, since there was also an increased incidence of cleft palate (13 fetuses from 2 of 11 litters including 12 from 1 litter) at 0.1 mg/kg/day in a previous study (TT #84-722-1). Single fetuses in the 0.015 and 0.03 mg/kg/day groups had cleft palate. These findings are not considered treatment-related since they were within the range of historical control and no cleft palates were caused by treatment in previous studies at 0.05 mg/kg/day (TT #84-710-0) and 0.06 mg/kg/day (TT #85-710-0).

There were slightly increased incidences of exencephaly usually associated with open eyelid in the 0.015 (2 fetuses from 2 of 24 litters), 0.03 (5 fetuses from 2 of 23 litters) and 0.5 (2 fetuses from 2 of 23 litters) mg/kg/day groups compared to the control (1 fetus from 23 litters).

The occurrence of exencephaly is not considered compound-related since it was not dose-related and was within the range of historical controls.

Other external malformations (open eyelid without exencephaly and cleft lip at 0.1 mg/kg/day and micrognathia and tail malformation at 0.5 mg/kg/day) are not considered treatment-related since they occurred in single fetuses and have been observed in historical controls.

Visceral examination showed single fetuses with interrupted aortic arch at 0.5 mg/kg/day and agenesis of the testes at 0.015 mg/kg/day. These visceral findings are not considered treatment-related since they occurred at single instances.

There was no evidence of treatment-related malformations or fetotoxicity in skeletal evaluations. There was no doseresponse for any single skeletal alteration which occurred at incidences comparable to historical controls. Historical control data are shown below.

MSDRL Historical Control Incidences of Selected Final Alterations in CF_1 Mice

Alteration	Fetuses Examined	Litters Examined	Fetuses with Alteration (%)	Litters with Alteration (%)
Exencephaly				
Overall	25,298	2142	69 (0.27)	59 (2.75)
TT #78-711-0[a]	428	35	7 (1.64)	5 (14.3)
Open Eyelid				
Overall	25,298	2142	52 (0.21)	47 (2.19)
TT #78-711-0[a]	428	35	4 (0.94)	3 (8.57)

[a] Study with highest incidence of indicated alteration.

MSDRL Historical Control Incidences of Selected Final Alterations in CF_1 Mice (cont'd)

Alteration	Fetuses Examined	Litters Examined	Fetuses with Alteration (%)	Litters with Alteration (%)
Micrognathia				
Overall	25,298	2142	8 (0.03)	8 (0.37)
TT #80-714-0[a]	288	24	2 (0.69)	2 (8.33)
Cleft Lip				
Overall	25,298	2142	1 (0.004)	1 (0.047)
TT #75-707-0[a]	416	30	1 (0.24)	1 (3.33)
Cleft Palate				
Overall	25,298	2142	69 (0.27)	63 (2.94)
TT #84-703-0[a]	235	21	3 (1.28)	3 (14.3)
Tail Malformation				
Overall	25,298	2142	5 (0.02)	5 (0.23)
TT #70-705-0[a]	224	18	1 (0.45)	1 (5.56)
Misshapen Rib				
Overall	16,383	1387	3 (0.018)	3 (0.22)
TT #73-700-0[a]	329	27	1 (0.30)	1 (3.70)
Cervical Rib				
Overall	16,383	1379	281 (1.71)	173 (12.5)
TT #79-712-0[a]	292	23	35 (12.0)	12 (52.2)
Incompletely Ossified Skull Bone				
Overall	11,653	1379	248 (2.13)	135 (9.79)
TT #76-723-0[a]	159	19	51 (32.1)	16 (84.2)
Incompletely Ossified Sternebra				
Overall	16,383	1387	170 (1.04)	112 (8.08)
TT #75-707-0	416	30	24 (5.77)	7 (23.3)
Cervical Vertebra Malformation				
Overall	16,383	1387	1 (0.006)	1 (0.072)
TT #79-714-0[a]	292	22	1 (0.34)	1 (4.55)
Thoracic Vertebra Malformation				
Overall	16,383	1387	13 (0.08)	13 (0.94)
TT #70-709-0[a]	159	18	2 (1.26)	2 (11.1)

[a] Study with highest incidence of indicated alteration.

MSDRL Historical Control Incidences of Selected Final Alterations in CF_1 Mice (cont'd)

Alteration	Fetuses Examined	Litters Examined	Fetuses with Alteration (%)	Litters with Alteration (%)
Missing Vertebra				
Overall	16,383	1387	39 (0.24)	29 (2.09)
TT #77-711-0[a]	416	35	6 (1.44)	4 (11.4)
Fused Rib				
Overall	16,383	1387	7 (0.04)	7 (0.51)
TT #79-712-0[a]	292	23	1 (0.34)	1 (4.35)
Agenesis of Rib				
Overall	16,383	1387	7 (0.04)	7 (0.51)
TT #79-799-0[a]	72	6	1 (0.34)	1 (16.7)
Hypoplastic Rib				
Overall	16,383	1387	11 (0.07)	9 (0.65)
TT #75-702-0[a]	433	38	3 (0.69)	2 (5.260
Lumbar Rib				
Overall	16,383	1387	712 (4.35)	374 (27.0)
TT #79-703-0[a]	293	24	24 (8.19)	13 (54.2)
Incompletely Ossified Cervical Vertebra				
Overall	16,383	1387	3 (0.018)	2 (0.14)
TT #85-701-0[a]	200	22	2 (1.00)	1 (4.55)
Incompletely Ossified Sacral Vertebra				
Overall	16,383	1387	5 (0.03)	5 (0.36)
TT #83-702-0[a]	230	20	2 (0.87)	2 (10.0)
Sternebral Variation				
Overall	16,383	1387	492 (3.00)	332 (23.9)
TT #70-709-0	159	18	38 (23.9)	17 (94.4)

[a] Study with highest incidence of indicated alteration.

Conclusion: The NOEL for maternotoxicity is 0.1 mg/kg/day for the 8,9-isomer of Abermectin. This NOEL is the same as that determined in a previous study (TT #84-722-1). The LEL for cleft palate is 0.1 mg/kg/day. The NOEL for teratogenic effects is 0.05 mg/kg/day in TT #84-722-1, 0.06 mg/kg/day in TT #85-710-0, and 0.03 mg/kg/day is the present study (TT #85-710-1). Therefore, the overall NOEL for teratogenicity is 0.06 mg/kg/day. The LEL for teratogenicity is 0.1 mg/kg/day.

Classification: Minimum.

IV. Volume III; Dietary Exposure and Risk Assessment for Abamectin (Accession No. 265565)

A. Merck has submitted for consideration a position document on abamectin. This document presents a summary and quantification of the teratogenic risks presented by abamectin for use on citrus.

Menu Screen Analysis: Females > 13 Years

Analysis of Proposed Residues: assuming that all food contain the residue at the level of detection or proposed anticipated residue

Menu Category	Maximum Residue (ppm)	Percent Of Exposure (%)
1. Meats	0.0050	31.03
2. Dry Beans, Peanuts	0	0
3. Eggs	0	0
4. Milk: Nonfat	0.0006	6.01
5. Milk: Fat	0.0006	3.28
6 Grains	0	0
7. Starch Vegs. + Rice	0	0
8. Tomatoes	0	0
9. Other Vegetables	0	0
10. Fruits	0.0050	59.69
11. Nuts and Seeds	0	0
12. Sugars	0	0
13. Misc. Foods	0	0

Total Exposure = 0.000038 mg/kg/bw/day.
Lowest NOEL (teratogenicity) = 0.06000 mg/kg/bw/day.
MOS for Teratogenicity = NOEL/Total exposure = 0.0600/0.000038
= 1579.

B. Menu Screen Analysis: Females > 13 Years

In the memorandum from D. Stephen Saunders of RCB to G. LaRocca (dated March 10, 1987), the TAS system was applied to the menu analysis for females 13 years and older.

A MOS of 1200 was calculated for teratogenicity based on the teratogenic NOEL of the delta-8,9-isomer of 0.06 mg/kg/day. A MOS of 1200 correlates with the MOS of 1579 calculated by Merck, considering the change in the meat tolerance from 0.005 ppm to 0.01 ppm required by RCB.

005850

Classification: Supplementary.

V. Section C; Volume I (Accession No. 265566)

A. Section Cla

A 10-day dietary maternotoxicity study in mice (MSD; TT #83-705-1); submitted August 16, 1985; Pesticide Petition No. 5G3287. Supplemental information on clinical signs.

Clinical signs of toxicity in pregnant mice given MK-0936.

Dosage Group	Female No.	Clinical Sign	Day When Noted	
0.3 mg/kg/day (1 ppm)	83-0645	Slight tremors	4	
		Moderate tremors	5	Killed
		Severe tremors	6	on
		Lethargic	4,5,6	Day
		Squincy eyes	4,5,6	6
		Hunched back	6	
	83-0647	Slight tremors	4 to 7	Killed on
		Marked tremors	7	Day 7
	83-0650	Slight tremors	4	Killed on
		Moderate tremors	5,6	Day 7
		Squinty eyes	4 to 7	
		Lethargic	6,7	
		Marked tremors	7	
	83-0658	Squinty eyes	3 to 12	
0.6 mg/kg/day (2 ppm)	83-0662	Tremors	3 (killed same day)	
	83-0668	Tremors	2,3 (killed on day 3)	
		Sluggish	2,3	

Classification: Minimum.

B. Section Cl.b

Oral teratogenic evaluation in mice (MSD; TT #77-705-0); submitted February 1982, 618-EUP-10; Supplemental skeletal examinations.

Fetal skeletons from the 0.1 and 0.2 mg/kg/day groups from TT #77-705-0 (Accession No. 246894) were examined. No treatment-related effects were observed.

Conclusion: Teratogenic LEL = 0.4 mg/kg (cleft palate); teratogenic NOEL = 0.2 mg/kg.

Classification: Minimum.

VI. Section C4; Volume IV (Accession No. 265567)

Acute oral toxicity studies with abamectin (MK-0936) in pregnant and nonpregnant mice (TT #84-2842; TT #85-2593; June 23, 1986).

A. MK-0936; I. Five-Day Acute Oral Toxicity Study in Pregnant and Nonpregnant CF_1 Mice (MSD; TT #84-2842; September 6, 1985)

Test Material: L-676, 863-00050 (MK-0936) purity 94% by HPLC; Avermectin B_1 CO76 B_1a and B_1b; sesame oil; Fisher's #746, 289.

Groups of 10 females each for nonpregnant group and 12 females for the pregnant group (10-12th day of gestation) received a single oral dose by gastric intubations of test material at dosages of 5, 10, 20, 40, and 80 mg/kg. The test period, following the single oral dose, was 5 days. All animals were examined when found dead or at the end of the 5-day test period to confirm pregnancy.

Results:

Pregnant Mice

LD_{50} = 19.0 mg/kg (14.0 to 25.7)

Nonpregnant Mice

LD_{50} = 41.3 mg/kg

Toxic Signs: Time of death was 73 minutes to 4th day. Within 1 hour of dosing tremors and bradypnea were seen at all dose levels in the nonpregnant mice and all but the lowest dose level (5 mg/kg) in the pregnant mice. Death was preceded by loss of righting reflex.

Conclusion: Based on this preliminary study, pregnant mice appear to be more sensitive to acute doses of MK-0936 than nonpregnant mice.

Classification: Minimum.

B. MK-0936; II. Five-Day Oral Acute Toxicity Study in Pregnant and Nonpregnant CF_1 Mice (MSD; TT #85-2593; September 6, 1985)

Test Material: MK-0936; purity 94% by HPLC.

Eleven-week-old pregnant and nonpregnant CF_1 mice, 24 to 41 g, were used in the study. Groups of 19 or 20 pregnant and 20 nonpregnant mice were used at each dose level (5, 10, 20, 40, and 80 mg/kg). Single oral doses of test material were administered by gastric intubation. Observation was for 5 days.

Results: The LD_{50} values (based on a 5-day mortality response):

Pregnant Mice

LD_{50} = 11.8 (8.3 to 15.8) mg/kg

Nonpregnant Mice

LD_{50} = 15.0 (10.2 to 21.1) mg/kg

Toxic Signs: In the pregnant mice, within 30 minutes, tremors, clonic convulsions, and bradypnea were seen in scattered mice at all dose levels. Tremors, bradypnea, and decreased activity were seen on the 2nd and 3rd day at doses of 20 mg/kg and above.

Deaths, which were preceded by loss of righting, occurred in 45 minutes to the 4th day. One mouse at the 10 mg/kg dose was not pregnant.

In nonpregnant mice, loss of righting and bradypnea were seen in scattered mice at all dose levels. On the 2nd day; tremors were seen at doses of 10 mg/kg and above. At the 80 mg/kg dose, decreased activity, bradypnea, ataxia and decreased activity were seen at doses of 20 mg/kg and above. Deaths occurred in 36 minutes to the 3rd day.

There were no toxic signs or death in either the pregnant or nonpregnant control mice that received the vehicle alone (sesame oil). Body weights were unaffected during the 5-day study.

Conclusion: It appears that pregnant mice may be slightly more sensitive to MK-0936 than nonpregnant mice.

Classification: Minimum.

VII. MK-0933 and MK-0936; Oral Toxicity and Plasma Level Study in Monkeys (Accession No. 265571) (MSD; TT #85-013-0; December 6, 1985)

The objective of the study was to establish the minimum effect level of MK-0933 (Ivermectin) and MK-0936 (Avermectin) in monkeys and to compare plasma levels of the two compounds at the minimum effect level. Also, the study was extended to higher dose levels to characterize more severe clinical signs of toxicity produced by these compounds in monkeys.

Single oral doses of MK-0933 or MK-0936 were given as solutions by gavage in sesame oil to groups of 2 male and 2 female rhesus monkeys each at intervals every 2 to 3 weeks.

The following doses were tested in chronological order: 0.2, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, and 24 mg/kg body weight. The ability of the compounds to cause mydriasis was evaluated by observing pupillary responses to a penlight at 2, 4, 6, and 24 hours following each dose.

Physical signs were observed daily and body weights were measured weekly.

Blood samples were taken from the femoral vein or artery of all animals at 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, and 96 hours following a dose of 2 mg/kg; at 8, 24, and 48 hours after a dose of 8 mg/kg and at 8, 24, 48, 72, and 96 hours following a dose of 24 mg/kg of each of the compounds for determination of plasma concentration. The plasma derived from these samples was analyzed by the modified LC-fluorescence method.

Results: No compound-related toxic signs were seen at doses of 0.2, 0.5, or 1.0 mg/kg of MK-0933 or MK-0936. The most sensitive indicator of toxicity was emesis. The incidence of emesis was dose-related and was similar for both compounds. The incidence is tabulated below:

Animal No.	Study Week: / Dose (mg/kg):	13 / 2.0	15 / 4.0	17 / 2.0	19 / 6.0	21 / 8.0	24 / 8.0	27 / 12.0	29 / 24.0
MK-0936									
84-0089					X	X	X	X	X
84-0091						X	X	X	X
84-0090		X	X	X		X	X	X	X
84-0092					X	X	X	X	X
Total		1	1	1	2	4	4	4	4
MK-0933									
84-0085			X	X	X	X	X	X	X
84-0087			X			X		X	X

Animal No.	Study Week: / Dose (mg/kg):	13 / 2.0	15 / 4.0	17 / 2.0	19 / 6.0	21 / 8.0	24 / 8.0	27 / 12.0	29 / 24.0
MK-0933 (cont'd)									
84-0086		X	X		X	X	X	X	X
84-0088			X		X	X		X	X
Total		1	4	1	3	4	2	4	4

In general, the time after dosing when emesis occurred tended to decrease as the dose increased, and was first seen at about 8, 4, and 2 hours following doses of 2.0, 4.0 to 12.0, and 24.0 mg/kg, respectively. Since no emesis occurred with doses below 2.0 mg/kg, and since no other compound-related toxic signs were observed at lower doses, it was concluded that emesis was the most appropriate toxic sign for characterizing minimum toxic doses of the compounds in monkeys, and that the minimum toxic dose was 2.0 mg/kg for both compounds.

Pupil dilation/decreased constriction was observed following doses of MK-0936 of 6.0 mg/kg and above and after doses of 12.0 and 24.0 mg/kg of MK-0933 as shown below:

Animal No.	Study Week: / Dose (mg/kg):	19 / 6.0	21 / 8.0	24 / 8.0	27 / 12.0	29 / 24.0
MK-0936						
84-0089		V. Slt	Mod	V. Slt	V. Slt	Mod
84-0091			Slt		Slt	Mkd
84-0090			Slt	V. Slt	Mod	Mkd
84-0092			Slt		Slt	Mkd
MK-0933						
84-0085						
84-0087						Slt
84-0086					Mod	
84-0088					Mod	

V. Slt (very slight) - Pupil dilation and/or slowed or incomplete pupil constriction seen at one eye exam.
Slt (slight) - Same response as above seen at two consecutive eye exams.
Mod (moderate) - Same response as above seen at three eye exams (2 to 24 hours).
Mkd (marked) - No pupil constriction seen at two or more eye exams.

Thus a lower incidence of mydriasis was observed by MK-0933 than by MK-0936 in this study. Therefore, mydriasis was not as sensitive an indicator of MK-0933 or MK-0936 toxicity in monkey as it was in dogs.

Both compounds induced slight to moderate sedation in 3 or 4 monkeys given 24.0 mg/kg.

Recovery from sedation was complete within 48 hours for all animals. The incidence and severity of sedation or decreased activity did not correlate with mydriasis. None of the monkeys became unconscious or comatose. No weight loss was observed and food consumption was normal during the study.

Plasma concentrations of MK-0933 and MK-0936 were roughly proportional to the administered dose. The plasma levels of MK-0933 and MK-0936 for individual animals did not correlate well with their toxic signs. The average plasma concentration following the dose of 2.0 mg/kg was highest at 8 hours for MK-0936 (76 ng/mL) and at 24 hours for MK-0933 (110 ng/mL).

Conclusion: The most sensitive indicator of MK-0933 and MK-0936 toxicity in the monkeys was emesis. A dose-related increase in the incidence of emesis occurred above 2.0 mg/kg, the minimal toxic dose. The NOEL for the study is 1.0 mg/kg.

Mydriasis was not as sensitive or reliable as an indicator of toxicity in monkeys as it was in dogs.

Slight to moderate sedation was observed in 3 out of 4 monkeys from both groups at the 24 mg/kg dose level. No tremors or convulsions occurred in any animals. Plasma level of drug increased with increasing dose.

Classification: Acceptable.

VIII. Avermectin $B_{1}b$; Acute Oral Toxicity and Maternotoxicity Studies in Mice (Accession No. 265572)

A. Avermectin $B_{1}b$ (L-676, 896-00402); Acute Oral Toxicity Study in Mice (MSD; TT #84-107-C; January 9, 1985)

The acute oral toxicity of Avermectin $B_{1}b$ (L-676, 896-00402) was studied in male and female mice. Avermectin $B_{1}b$ is one of the two major components of MK-0936. The $B_{1}b$ component comprises a maximum of 20% of MK-0936. The $B_{1}a$ component comprises a minimum of 80% of MK-0936.

Test Material: Avermectin B_{1b} (L-676, 896-00402) 98.1% pure by HPLC; sesame oil, Fisher No. 700653.

Young adult albino male and female CF_1 mice weighing 22 to 25 g and 5 to 7 weeks old were used. Groups of 10 mice of each sex were gavaged at 5, 10, 20, 40, and 80 mg/kg. Observation was for 14 days.

Results:

Male

LD_{50} = 11.4 (7.6 to 16.1) mg/kg

Female

LD_{50} = 19.8 (12.8 to 31.0) mg/kg

Toxic Signs: The female mice given doses of 10 mg/kg and above within 30 minutes of dosing had signs of ataxia, tremors, bradypnea, and intermittent clonic convulsions. Tremors were seen at the lowest dose (5 mg/kg) in about 4 hours. From the 2nd through the 4th day, tremors, bradypnea, ataxia, and ptosis were seen at all but the lowest dose (5 mg/kg). Deaths which occurred from 27 minutes to the 6th day postdose were preceded by loss of righting. Signs in the male mice were generally similar except at the lowest dose (5 mg/kg) where all signs were seen rather than just tremors as seen in the female mice. Deaths in the male mice occurred from 33 minutes to the 6th day. Mice given the vehicle alone (sesame oil) had no abnormal signs and none died.

Necropsy: No gross changes were seen in any mouse at any dose level.

Toxicity Category I

Classification: Minimum.

B. Avermectin B_{1b}; II. Oral Maternotoxicity Study in Mice (MSD; TT #84-721-0; March 4, 1985)

Test Material: Avermectin B_{1b} (L-676, 896-004) Lot No. 02; purity > 98%, HPLC.

Groups of mated CF_1 female mice were used in the study.

Treatment Groups	Number of Females
Vehicle Control	12
0.025 mg/kg/day	12
0.05 mg/kg/day	12
0.075 mg/kg/day	12
0.10 mg/kg/day	12

Dosing was between days 6 through 15 of gestation orally by gavage.

Body weights were taken on days 0, 6, 8, 10, 12, 14, 16, and 17 of gestation. Females were sacrificed on day 17 of gestation and uterine contents were examined. Implants were counted and classified as resorptions, dead fetuses or live fetuses. All fetuses were weighed, sexed, and examined externally. Statistical analysis of the data were performed.

Results: There were two compound-related deaths in the 0.075 mg/kg/day group after 6 doses: one female was found dead on day 11 of gestation (84-0243) and another was killed in a moribund condition on day 12 of gestation (84-0237). There were no gross lesions. There were no other deaths. The two early death females in the 0.075 mg/kg/day group had treatment-related tremors when observed prior to dosing and approximately 3 to 5 hours after dosing on day 10 of gestation. There were no other clinical signs of toxicity. The two early death females in the 0.075 mg/kg/day group had compound-related decreases in body weight of 7.2 and 6.6 g prior to deaths.

There were no effects on body weight gain in other mice.

There were no compound-related effects on fetal survival or live fetal weight.

There were slight but not significant ($P > 0.05$) increases in the resorption rate at 0.075 and 0.1 mg/kg/day (10.3 and 8.9%, respectively) compared to controls (4.1%) which are not considered treatment-related. The control group from a study conducted concurrently (TT #84-722-0) had a resorption rate equal to the highest value on this study (10.3%).

One fetus at 0.025 mg/kg/day and one fetus at 0.10 mg/kg/day had exencephaly. One fetus at 0.05 mg/kg/day and one fetus at 0.075 mg/kg/day had cleft palate. No control fetuses had malformations.

Since exencephaly and cleft palate are spontaneous anomalies in this strain of mice, these findings are not considered treatment-related.

Conclusion: The NOEL for maternotoxicity of Avermectin B_1b was 0.05 mg/kg/day.

The LEL was 0.075 mg/kg/day and the effect was mortality in two mice after 6 doses.

Classification: Acceptable.

IX. MK-0936 (Avermectin B_1)

A. Microbial Mutagenesis Assay (MSD; TT #85-8051; March 11, 1986; Accession No. 265568)

Test Material: MK-0936 (L-676, 863-00V50); purity 94% by HPLC.

Ames Assay: The test material was tested at dosages of 3, 10, 30, 100, and 1000 ug/plate with and without metabolic activation (S-9). The test material was tested up to solubility limits (1000 ug). Mutant strains of Salmonella typhimurium used were TA98, TA100, TA1535, TA1537, and TA1538. Positive controls were tested. The assay was run in triplicate.

Results: MK-0936 did not induce twofold or greater dose-related increases in revertants and is not mutagenic.

Conclusion: MK-0936 is not mutagenic in the Ames Assay.

Classification: Acceptable.

B. MK-0936 (L-676, 863-00V54); Avermectin B_1, Microbial Mutagenesis Assay (MSD; TT #85-8005; May 1, 1986; Accession No. 265569)

Test Material: MK-0936 (L-676, 863-00V54); Avermectin B_1; purity 89% on w/w basis.

Ames Assay: The test material was tested at dosages of 100, 300, 1000, 3000, and 10,000 ug/plate without metabolic activation (S-9). The test material was tested up to solubility limit (1000 ug). Mutant strains of Salmonella typhimurium used were TA98, TA100, TA1535, TA1537, and TA1538. Positive and negative controls were tested. The assay was run in triplicate.

Results: MK-0936 (L-676, 863-00V54); Avermectin B_1, did not induce twofold or greater dose-related increases in revertants and is not mutagenic without metabolic activation.

Conclusion: MK-0936 is not mutagenic in the Ames Assay without metabolic activation. The system was not tested with metabolic activation.

Classification: Acceptable (when considered with TT #85-8051, above).

C. Avermectin B_1 (MK-0936); Assay for Chromosomal Aberrations In Vitro in Chinese Hamster Ovary Cells (MSD; TT #85-8631, 8632, 8635; March 11, 1986; Accession No. 265570)

Test Material: Avermectin B_1; MK-0936; L-676, 863-00V50; purity; 94% by HPLC; Composition B_1a: 84.05; B_1b: 13.0%.

	TT No.
Range-Finding I	85-8631
Range-Finding II	85-8632
Chromosomal Aberrations	85-8635

In study 8631, cytotoxicity (less than 10% cell survival at 0.03 mM with metabolic activation, but not cytotoxic up to 0.01 mM without metabolic activation).

In study 8632, a repeat of study 8631 without metabolic activation at higher concentrations. The system was cytotoxic (50% cell survival) at highest concentrations, 0.02 to 0.035 mM.

In main assay, study 8635, the doses of test material used were 0.01, 0.015, 0.02, 0.025, 0.030, and 0.035 mM without activation and 0.005, 0.01, 0.015, 0.02, and 0.025 mM with activation.

The treatment was 3 hours with and without metabolic activation.

Sampling was at 10.5 and 24 hours postfixing.

Appropriate controls and procedures were used.

Results: Negative for aberrations up to cytotoxic levels.

Conclusion: MK-0936 was not mutagenic in the chromosomal aberrations in vitro, Chinese hamster ovary cells test.

Classification: Acceptable.

X. MK-0936; Reproductive Effects of MK-0936 Administered Orally by Gavage to Crl: COBS CD (SD) BR Rats for Two Generations (TT #82-9010; May 10, 1984; Argus Research Labs (antemortem phase) and MSDRL (postmortem phase)). Accession No. 265576.

Test Material: MK-0936, Lot #L-676, 863-00V50; vehicle, sesame oil; Lot #720376; Lot #731005 MK-0936 was provided by the Sponsor Merck as a 6.0 mg/mL stock solution in sesame oil. Rats were given the test agent orally (by gavage), once daily, at dosages of 0 (vehicle), 0.05, 0.12, and 0.40 mg/kg/day. All dosages were given to rats at a volume of 5 mL/kg/day.

A. Antemortem Phase

Randomized groups of 30 male and 30 female Sprague-Dawley rats were assigned to a vehicle control (sesame oil), and dosages of 0.05, 0.12, and 0.40 mg/kg/day of test material. Intubation with either the vehicle or MK-0936 was initiated daily when these rats were 39 days old and had individual body weights ranging from 142 to 194 g (male rats) and from 113 to 151 g (female rats). Daily dosing was continued until death.

F0 rats were mated twice, in order to produce two litters, the F1a and the F1b. The F1b litters were also mated twice to produce two litters, the F2a and F2b.

F0 male rats were given the test material for a total of 259 days. The dosage period for F0 male rats included 68 days prior to cohabitation, 42 days during the two cohabitation periods, 42 days during the two gestation periods, 42 to 51 days during the F1a and F1b lactation periods, at least 16 days during a maternal rest period and approximately 50 days after the last F1b pup was weaned.

F0 female rats were given the test material for a minimum of 177 days. This dosage period included approximately 68 days prior to cohabitation, 42 days during the cohabitation periods, approximately 42 days during the F1a and F1b gestation periods, 42 to 51 days during the F1a and F1b lactation periods and at least 16 days during a maternal rest period.

At weaning of the F1b rats, five males and five female pups per dosage group were selected and sent to the

sponsor for subsequent complete gross necropsy and histopathology evaluations. Also at weaning, one or two male and one or two female pups from each F1b generation litter with surviving pups (a total of 32 male and 32 female pups per dosage group) were randomly selected for continued study.

The intubation period of the F1b generation began at weaning and continued for a maximum of 273 days. This period included at least 70 days prior to cohabitation, up to 42 days during the two cohabitation periods, approximately 44 days during the two gestation periods, approximately 45 days during F2a and F2b lactation periods, at least 14 days during a maternal rest period, and at least 30 days after the last F2b pups were weaned.

The F1b generation rats were also mated twice to produce two litters, the F2a and the F2b. The first cohabitation period began when the F1b generation animals were approximately 100 days old (after at least 70 days of intubation), and procedures similar to those used for production and selection of the F1a and F1b litters were used. A table of random numbers was used to select 10 male and 25 female F1b generation animals per dosage group for evaluation by the Sponsor using complete necropsy and histopathology procedures. The testes and epididymides from remaining F1b male rats were removed, weighed, and fixed; eyes were retained from these F1b male rats and from the remaining F1b female rats. These tissues were sent to the Sponsor.

At weaning of the F2b rats, a table of random numbers was used to select ten male and ten female weanling rats per dosage group for skeletal examination at the Test Facility, and five male and five female F2b weanling rats per dosage group for complete gross necropsy and histopathology evaluations by the Sponsor. The eyes from the F2a and F2b weanling rats were excised at sacrifice and sent to the Sponsor.

Clinical observations, body weights and reproductive parameters were recorded for the F0 and F1b rats. Mating confirmations, delivery and lactation observations, as well as pup viability, sex, and body weights were recorded for the F1a and F1b rats until weaned; the same procedures were followed for the F2a and F2b rats. A gross external and visceral examination was performed on pups which died during the lactation period and they were examined for skeletal anomalies.

Statistical analyses of the data were performed.

Results: During the period F0 generation rats were administered the MK-0936, nine rats died or were sacrificed. The mortality was not dose-related and the deaths were not attributed to test material.

Death or morbidity occurred for 1, 2, and 2 F0 male rats given the vehicle, 0.05, or 0.12 mg/kg/day of MK-0936, respectively. No F0 male rats at the high dosage became moribund or died.

Two control and two 0.05 mg/kg/day F0 female rats died. No mid- or high-dose F0 female rats died.

There were no compound-related clinical observations for F0 male or female rats during the study.

In the mid- and high-dose F0 male rats, increased body weight gains occurred from day 7 to day 259 for high-dose rats and from day 7 to day 77 for mid-dose male rats.

In the mid- and high-dose F0 female rats, increased body weight gains were observed during the day 7 to day 63 growth phase.

During the F0 to F1a gestation period, increased body weight gains were observed in the mid- and high-dose F0 dams. However, as in the F1a gestation period, the body weight change from days 0 to 20 of the F1b gestation period did not show any increases between control and treated dams.

The body weight of dams with live pups during the F1b lactation period showed less increased body weight gain during days 1 through 22 for the mid- and high-dose dams in comparison to controls.

With respect to mating and fertility data, male rats of the F0 to F1a generation showed no compound-related effects on male rats which mated, or days in cohabitation.

Male rats of the F0/F1b generation showed a significant decrease ($P < 0.01$) in mating at the high-dose in comparison to controls (89.3% in controls mated compared with 63.3% in high dose which mated). Average testes and epididymides weights were similar for all F0 male rats. Additionally there was a dose-related increase in days in cohabitation for male rats at all dosage groups as shown on the following page.

Male/Rats Flb Generation

	Dosage Group (mg/kg/day)			
	0	0.05	0.12	0.40
Days in Cohabitation (mean ± S.D.)	2.6±2.7	4.1±3.6*	4.4+3.2**	7.2±5.8**

* $p < 0.05$.
** $p < 0.01$.

In female rats of the F0 to Fla generation, there were no effects on fertility, days in cohabitation, or length of gestation. However, there was a significant increase ($p < 0.01$) at the high-dose in surviving dams with all live born pups dying (4.2% in control versus 28.0% at high-dose). This effect occurred primarily at days 8 through 14 postpartum. Additionally at the high-dose in the Fla litters, pup mortality (42.2%), decreased viability indices and decreased lactation index were observed. Pup body weight at the high-dose was significantly decreased ($p < 0.01$) at days 7, 14, and 21 in comparison to controls. Summary of Fla gross litter observation showed an increased incidence of high-dose litters with pups which were thin and not nursing.

In female rats of the F0 through Flb generation there was a significant decrease in female rats which mated at the high-dose (100% in controls vs. 73.3 percent in high-dose; $p < 0.01$). Also at the high-dose, a significant increase in days of cohabitation occurred in female rats (3.8 ± 4.8 days in control vs. 9.5 ± 8.7 days at high-dose).

However, the fertility index (mated female rats which littered) was 75.0 percent, 79.3 percent, 86.7 percent, and 72.7 percent for the control, low-, mid-, and high-dose groups, respectively. Additionally, there was no effect of treatment of the duration of gestation in the Flb generation.

At the high-dose in the Flb litters, there was an increase in surviving dams with all liveborn pups dying (0% in controls vs. 25.0% in high-dose), increase in total pup mortality (2.0% in controls vs. 33.1% in high-dose), decreased viability index (days 4 through 14) and lactation index (98% in control vs. 60% in high-dose). Pup body weight at the high-dose was significantly decreased ($p < 0.01$) at days 7, 14, and 21. Summary of Flb gross litter observations showed an increased incidence of high-dose litters with pups which

were thin and not nursing. No compound-related skeletal anomalies were observed in F1a or F1b pups which were found dead during the lactation period.

Five F1b rats selected for the second generation died or were moribund sacrificed, but the deaths were not dose-related.

Two low-dose and one high-dose F1b male rat died and one mid-dose F1b male rat was sacrificed moribund. No control F1b male rats died. One low-dose F1b female rat died.

No compound-related toxic signs were observed in F1b male or female rats during the study.

High-dose F1b male and female rats selected for the second generation had smaller average body weights than control F1b rats when individual intubation was initiated. This effect was also observed for mid-dose F1b female rats selected for the second generation.

High-dose F1b male rats continued to have decreased body weight up to day 28 ($p < 0.01$). Between day 28 and day 168, high-dose F1b male body weight was comparable to controls. Between days 175 to 238 the body weight of high-dose F1b males was significantly higher than controls. From day 245 to completion of the treatment at day 272, high-dose F1b male body weight was higher than controls but not significantly. Body weight changes were comparable between control, low, and mid-dose F1b males during the study.

Body weight of F1b female rats during the 84-day growth phase were comparable between control, low, and mid-dose groups and slightly lower for the high-dose group.

Body weight gain of the F1b females during the F2a gestation period were significantly higher during the first nine days for the mid- and high-dose females, but the body weight change between days 0 to 20 percent gestation were comparable between control and treated groups.

During the subsequent lactation period (F1b/F2a), body weight change was decreased in mid- and high-dose F1b females during days 0 through 10, but were comparable between groups by day 20.

Body weight change of the F1b females during the F2b gestation period were comparable between control and treated animals.

Body weight change of the F1b females during the F2b lactation period were slightly less for the high-dose females in comparison to the control during the 22-day period.

Male rats of the F1b/F2a generation showed no compound-related effects in fertility, days in cohabitation, or other reproductive parameters.

Male rats of the F1b/F2b generation showed no compound-related effects in fertility. In days in cohabitation, males rats of the high-dose which mated showed significant differences in comparison to the controls as shown below:

Male Rats Mating (%)	Dosage Group (mg/kg/day) 0 (vehicle)	0.05	0.12	0.40
Days 1-4	63.6	52.4	40.9	90.9*
Days 5-8	13.6	0*	27.3	9.1*
Days 9-14	22.7	47.6	31.8	0

* $p < 0.05$.

Testes and epididymides weights were comparable between control and treated F1b rats.

In F1b female rats of the F2a generation, there were no compound-related effects in female rats which mated, days in cohabitition, fertility index and duration of gestation.

In the F2a litters, there was an increase in total pups dying at the high-dose (1.8% in controls vs. 6.7% in high-dose). Additionally, there was a significant decrease in days 4 through 14 viability index and lactation index at the high-dose in the F2a litters. Also observed at the high-dose in the F_2a litters was a significant decrease in pup body weight at days 7, 14, and 21.

Summary of gross litter observations of the F2a litters showed an increase incidence of high-dose litters with pups which were thin, not nursing or weak.

In the F1b female rats which produced the F2b generation, there were no compound-related effects in female rats which mated, days in cohabitation, fertility index and days of gestation. There was a significant increase at the high-dose in female rats mated by the first male during days 1 through 4.

In the F2b litters, there was a significant increase in total pups dying at the high-dose (8.6%) in comparison to controls (4.2%).

Additionally, there was a significant decrease in the days 4 through 14 viability index, and lactation index in high-dose pups of the F2b litters. Pup body weight was significantly decreased at the high-dose at days 7, 14, and 21 of the F2b litters.

Summary of F2b gross litter observations showed a higher incidence of high-dose litters with pups which were cold to touch, thin, not nursing, and weak.

Skeletal evaluation of F2a and F2b pups found dead during the lactation period did not show any compound-related effects. Skeletal examination of 20 F2b weanlings per dosage group did not show any skeletal anomalies.

B. Section B - Postmortem Report

The objective of the postmortem study was to assess abnormalities in organ weights or histomorphology of F0 adults, F1b weanling, F1b adults, and F2b weanlings. The pathological examinations were conducted by Merck.

(1) Postmortem Report of F0 Adults

There were no treatment-related deaths. Nine rats died or were sacrificed prior to scheduled necropsy: 3 controls (95, 121, 190 doses), 4 given 0.05 mg/kg/day (143, 168, 171, 203 doses), and 2 given 0.12 mg/kg/day (103 or 216 doses). Causes of death included intubation accident (2), lymphocytic lymphoma (1), pyelonephritis (1), metritis (1), and renal tubular degeneration (1). There were no early deaths among rats given 0.40 mg/kg/day.

Results: There were no drug-related histologic changes in F0 adults examined at necropsy; the number of F0 rats necropsied were 14, 4, 2, and 14 in the control, low-, mid-, and high-dose groups, respectively.

(2) F1b Weanlings

Five male and five female weanlings were selected randomly from the F1b litters in each treatment and control group. One selected male in the high-dose group died before scheduled necropsy so that group is missing one animal.

Rats were necropsied and organ weights and tissues were examined histologically.

Body weights and weights of liver, kidney, testes, heart, brain, and spleen were recorded for all except two mid-dose animals. In these cases the body weight was not recorded at necropsy so the organ weights were not entered into the record. An extensive list of tissues from all rats were examined histologically.

Results: No treatment-related organ weight changes were noted. There were several pups in the high-dose group that were considerably smaller than those in the control. Treatment-related retinal anomalies were seen in 3/4 males and 1/5 females in the high-dose group. The incidence was 1/10 in the control group and 1/10 in low and 1/10 in mid-dose group. The anomalies were in the form of single or multiple retinal folds of many layers that included pigment epithelium in the center. Some appeared as intra-retinal rosettes and in others the connection into the pigment layer was seen in the section.

(3) F1b Adults

Twenty-five female and ten male F1b adults were randomly selected for necropsy at 42 to 43 weeks of age. A complete necropsy examination was done on all rats following sacrifice by ether anesthesia and exsanguination. Terminal body weight and the following organ weights were recorded: brain, spleen, heart, kidneys, liver, and testes. Tissues were fixed in neutral buffered formalin and examined histologically.

Results: There were no deaths attributable to treatment. Seven rats died prior to scheduled necropsy; 2 control male rats were staggering upon arrival at Merck for scheduled sacrifice and died overnight; they had no abnormal signs before leaving Argus Labs. A cause of death was not determined in either case. Five other treated rats died before scheduled necropsy and they had the following observations:

Group	Necropsy ID No.	Doses	Significant Findings or Cause of Death
0.05	118463 male	141	Abscess-next to thoracic inlet
0.05	119499 male	189	Slight hepatocyte vacuolation

Group	Necropsy ID No.	Doses	Significant Findings or Cause of Death
0.05	119498 female	189	Advanced pregnancy- 15 pups and 1 resorption
0.12	120744 male	262	Malignant neuroblastoma
0.40	116378 male	30	Moderate focal hepatic necrosis; possible intubation accident.

There were no treatment-related effects in organ weights. There were not treatment-related gross or histological changes in the remaining examined F1b adult animals.

The incidence of pituitary adenomas observed in the male animals was not considered compound-related. The incidence was as follows:

	Dosage mg/kg/day			
	0	0.05	0.12	0.40
Adenomas in Males	0/8	1/9	1/10	2/10

These rats were approximately 42 through 43 weeks old at the time of necropsy.

(4) F2b Weanlings

F2b weanlings were born at Argus Labs and were necropsied at weaning when they were 22 to 25 days old. Five male and five female weanlings were randomly selected from F2b litters in each treatment and control group. Body weights and organ weights were taken and tissues were examined histologically.

In addition, more eyes were processed from all dosage groups; control; 46 females, 52 males; low-dose, 29 females and 21 males; mid-dose: 81 females and 83 males; high-dose; 61 females and 58 males.

Results: There were no compound-related effects in organ weights. There was a statistically significant increase in retinal anomalies in the high-dose group.

The incidence and type of eye lesion is shown below.

	Dosage mg/kg/day							
	Control		0.05		0.12		0.40	
	M	F	M	F	M	F	M	F
Nc. Examined	57	51	26	34	88	86	63	66
Retina anomaly	3	2	0	1	5	2	10	18
Retina hemosiderosis	0	0	0	0	0	0	0	1
Keratitis	0	0	0	0	0	0	0	1

The anomalies were in the form of single or multiple retinal folds of many layers that included pigment epithelium in the center. Some appeared as intra-retinal rosettes and in others the connection with the pigment layer was seen in the section. This change was also seen in 4 of 9 high-dose F1b weanlings (versus 1 of 10 in controls), however, only 1 of 35 high-dose F1b adults had a retinal anomaly and none of 33 controls has this change.

Conclusion: Retinal anomalies are a treatment-related effect in the high-dose group F1b and F2b weanlings. The NOEL appears to be 0.12 mg/kg/day. The overall NOEL for the study may be also 0.12 mg/kg/day. At the possible LEL of 0.40 mg/kg/day (high-dose), there were several effects in the study:

a. Decreased number of male rats which mated as F0/F1b adults.

b. Increase in surviving dams with all pups dying in F0/F1a litter.

c. Increased pup mortality, decreased viability indices, decreased lactation indices and decreased pup body weight in the F1a, F1b, F2a, and F2b litters.

Additionally, TB requires that all histological slides of both eyes of all F0 adults, F1b weanlings, F1b adults, F2a weanlings, and F2b weanlings of this study be submitted for additional evaluation. Additionally, the litter should be identified for the examined weanlings.

Classification: Supplementary (pending submission of the above slides).

XI. MK-0936; I. Fifty-Three-Week Dietary Toxicity Study in Dogs (MSDRL TT #82-104-0; April 24, 1984). Accession No. 265574

Test Material: MK-0936 (identified as L-676, 863-00V54) used throughout the study; all assays were found to be within acceptable limits (better than 89% total B_{1a} and B_{1b}, using HPLC).

A. Antemortem Phase

Twenty-four male and 24 female beagle dogs, aged 20 to 24 weeks at initiation, were used in the study. Males ranged from 5.4 to 8.7 kg and females ranged from 4.9 to 7.4 kg body weight. Dogs were individually housed in an environmentally controlled room. Purina Certified Dog Chow, in meal form was supplied daily and water was available ad libitum. Food was withdrawn approximately 17 hours prior to necropsies and bleedings. MK-0936 was mixed with the diet at concentrations calculated to provide nominal dose rate; mixing was done by Biodynamics, Inc., based on calculations made biweekly. The test material was dissolved in acetone, and mixed into approximately 1.5 kg of diet; acetone was allowed to evaporate; the premix was then mixed with additional meal to provide two 35 kg batches of feed with the correct final concentration. Aliquots of feed were taken periodically, and were found to be within acceptable limits.

The following treatment groups were initiated:

Treatment Group	Males	Females
Control	6	6
0.25 mg/kg/day	6	6
0.50 mg/kg/day	6	6
1.0 mg/kg/day	6	6

The doses were selected on the basis of the results of a range-finding study (TT #82-073-0).

Approximately 400 g of feed was provided to each dog daily; due to drug-related inacceptance in females receiving 1.0 mg/kg/day, beginning in drug week 36, the amount of treated meal was reduced (by approximately 50%) and the dogs were supplemented with approximately 200 g of canned dog food. Since food consumption improved with this regimen, the same procedure was instituted for male dogs at the same dose level in week 39. Drug concentrations in feed were adjusted to maintain the intended dose of 1.0 mg/kg/day.

The animals were examined daily for signs of drug effect with less detailed examinations on weekends and

holidays. On weekdays (except holidays), dogs were examined to determine whether there was miosis (pupillary constriction) from light stimulus (penlight).

Dogs were weighed once weekly and food consumption was measured four times weekly.

Ophthalmologic examinations were conducted in pretest and at weeks 12, 25, 40, and 52 by indirect ophthalmoscopy on all dogs.

Hematologic examinations were made on all dogs at pretest and in weeks 4, 8, 12, 26, 38, and 52 from blood samples taken from the jugular veins.

Measured parameters included: erythrocyte count, erythrocyte sedimentation rate, mean corpuscular volume, hemoglobin, activated partial thromboplastin time, total and differential leukocyte counts, differential leukocyte counts, platelet counts and the following calculated parameters; hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Serum biochemical examinations were conducted at the same time and included: total protein, glucose, creatine, SGOT, triglycerides, albumin, BUN, sodium, SGPT, potassium, chloride, alkaline phosphatase activity, cholesterol, ionized calcium, and direct and total bilirubin.

Urinalyses were collected overnight from all dogs, pretest and in weeks 4, 8, 12, 26, 38, and 52 and included glucose, protein, bilirubin, occult blood and microscopic examination of sediment.

Results: There were no tables or data presented for physical signs.

The report states that "there was absence of or at least decreased contribution of pupils to light in dogs receiving 1.0 mg/kg/day and those receiving 0.5 mg/kg/day. It was noted 422 times at the top dose level (an occurrence rate of approximately 15%), and 101 times at the middle dose (an occurrence of approximately 3%). It was also seen a total of four times at the low dose level (twice each in two dogs). Although this mydriasis was seen at least once in all dogs receiving 1.0 mg/kg/day and all but one dog receiving 0.5 mg/kg/day, there was little consistency; some dogs showed mydriasis frequently on five observation days and then not at all for the next observation period. This makes evaluation of the finding in the lowest dose group difficult to interpret, although the sign was never seen in controls, its appearance in only two days may be mere chance."

Three male dogs died in the high-dose group. Dog 82-0476 m was killed in week 33 due to weight loss and lethargy. Dog 82-0464 m showed excessive salvation unsteadiness and finally lateral recumbence before its sacrifice in week 38. Dog 82-0532 m was found dead in week 38 without preliminary symptoms. These three deaths were attributed to the test material.

Dog 82-0476 m showed weight loss beginning at week 22 (8.7 kg) to week 33 of death (6.9 kg).

The total weight change between pretest period 1 and weight obtained in drug week 52 was plus 5, 5, 5.7, 5.7, and 4.0 kg for all dogs in the control, low-, mid- and high-dose, respectively. The control dogs were 23 percent heavier than the high-dose dogs at the end of the study. Average drug consumption in mg/kg/day varied between 0.18 and 0.32 for the low-dose, 0.39 through 0.62 for mid-dose, and 0.68 through 1.22 for the high-dose. Individual values showed more variation than the averages.

Food consumption in g/day was decreased significantly for high-dose dogs in comparison to mid-, low-, and control dogs during most of the study. Dog 82-0464 m of the high-dose group which was killed in week 38 showed a 10.5 percent increase in nonsegmented neutrophils just prior to sacrifice. However, there were no other compound-related effects in hematological parameters.

There were slight decreases in BUN values in high-dose dogs in weeks 8, 12, 26, and 38 in comparison to mid, low, and control dogs. There also were slight decreases in total protein values in high dose dogs during weeks 12, 26, and 38 in comparison to other treated and control dogs. These biochemical decreases may be related to decreased food consumption observed during this period in high dose dogs.

Urinalyses examinations were unremarkable.

B. Postmortem Phase

At conclusion of the study, all remaining dogs were anesthetized, exsanguinated and given complete necropsy examinations. Weights of hearts, livers, brains, adrenals, kidneys, and testes were recorded. Histopathological examination of salivary gland, stomach, small intestine, large intestine, liver, gall bladder, pancreas, adrenals, thyroids (and parathyroids when present in sections) kidneys, pituitary, urinary bladder, ovaries/testes, uterus, prostate, skin (and mammary gland, when present in section) lung, hearts, spleen,

lymph node, thymus, bone and bone marrow, skeletal muscle, brain, spinal cord, nerve, eye, and optic nerve of each dog were carried out.

The absolute organ weights, organ weights expressed as percent of body weight and organ weights expressed as percent of brain weights did not show any compound-related effects.

There were no compound-related effects in gross necropsy or histopathology in male and female dogs (including the eyes).

Conclusion: A NOEL cannot be established based on the submitted data. TB requires complete detailed results of the physical examination of all dogs (control and treated) during the entire study to be submitted for evaluation. Additionally, TB requires that the ophthalmoscopic examinations of all dogs of pretest and in weeks 12, 25, 40, and 52 be submitted for evaluation.

Classification: Supplementary (pending submission of the above information).

XII. One-Hundred-Five-Week Dietary Carcinogenicity and Toxicity Study in Rats with a Fifty-Three Week Interim Necropsy (Interim Report) (MSDRL TT #82-099-0; March 23, 1984). Accession No. 265575

Test Material: MK-0936, Lot No. L-676, 863-00V54; 91.1% purity.

A. Antemortem Report

Outbred albino rats, Crl:CD (Sprague-Dawley) BR obtained from Charles River Laboratories, Wilmington, MA were used in the study. The rats were approximately 5 weeks old at initiation of the study. Males weighed between 115 through 191 g and females weighed between 93 and 143 g. Rats were housed in individual cages in clean air and temperature controlled rooms. Purina Certified Rodent Chow and water were available ad libitum. Food was withheld approximately 17 hours prior to bleedings and interim necropsy. Test material was mixed with the rodent chow in appropriate amounts at Biodynamics, Inc., East Millstone, NJ. All test diets were consumed within four weeks of preparation. Randomized groups of male and female rats were placed in the following treatment groups.

Treatment Groups*	Males	Females
Control I (acetone-treated feed)	65	65
Control II (acetone-treated feed)		
0.75 mg/kg/day	65	65
1.5 mg/kg/day	65	65
2.0 mg/kg/day	65	65

* Fifteen animals/sex/group were selected for the 53-week interim sacrifice prior to study initiation. The dosage level for the high-dose group was increased to 2.5 mg/kg/day in drug week 11. Due to the appearance of severe signs of CNS toxicity following the increase in dosage, the dose level for the high-dose group was decreased back to 2.0 mg/kg/day in drug week 13. To prevent excessive mortality the males and females in the high-dose group only were placed on control feed for one day in drug weeks 12 and 13, respectively. The following day the diets for the 2.0 mg/kg/day target dose levels were administered.

For the interim study males were maintained on the diet for 368 to 370 days and females for 371 to 372 days.

Doses were selected on the basis of results of a range-finding study (TT #82-075-0,-1)

All animals were given detailed physical examinations weekly, including examination for all palpable masses. Body weights were recorded pretest and weekly for all animals throughout the study. Food consumption was measured weekly over a 6-day interval for 12 animals/sex/group. Ophthalmic examinations were performed on all animals pretest and high dose and control animals only in drug weeks 26 and 52 (males) or 53 (females). Hematological examinations were conducted on 10 of the 15 animals/sex/group designated for interim sacrifice. Analyses were performed in drug weeks 12, 25, 38, and 51. Parameters evaluated included the following:

(1) Direct Determinations

Hemoglobin concentration
Erythrocyte count
Total leukocyte count
Differential leukocyte count
Erythrocyte sedimentation rate

Mean corpuscular volume
Clotting time
Platelet count

(2) Calculated Parameters

Hematocrit
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration

Serum biochemical determinations were conducted on 10 of the 15 animals/sex/group designated for interim sacrifice. Analyses were performed in drug week 12, 25, 38, and 51. Quantitative determinations were made on the following parameters: total protein, albumin, SAP, glucose, cholesterol, triglycerides, BUN, sodium, creatinine, potassium, calcium, SGPT, SGOT, bilirubin (direct and total). Due to insufficient serum samples, direct bilirubin determinations were not obtained in drug week 51.

Urinalyses were conducted on 10 of the 15 animals/sex/group designated for interim sacrifice. Analyses were performed in drug weeks 12, 25, 38, 40 (due to apparent contamination of urine samples collected in drug week 38 with feed and/or feces, urinalyses for all groups were repeated in drug week 40) and 51. The same animals were used for all clinical laboratory studies, whenever possible. Urine was collected overnight from rats placed in metabolism cages. Animals did not have access to feed during the urine collection interval. The following qualitative determinations were made: microscopic examination of sediment, glucose, protein, bilirubin, and occult blood.

Results: The total incidence of unscheduled deaths through drug week 53 is listed in the following table:

Unscheduled Deaths

Treatment Group	Found Dead		Sacrificed	
	M	F	M	F
Control I	1	3	2	0
Control II	2	1	0	0
0.75 mg/kg/day	1	1	1	1
1.5 mg/kg/day	2	1	0	0
2.0 mg/kg/day	1	1	5	1

"Compound-related tremors were noted in high-dose group animal Nos. 82-7691 F, 82-7741 F, 82-7742 M, and 82-7692 M in drug week 12. With the exception of animal No. 82-7691 F, which had tremors beginning in drug week 9, the

appearance of the effect in the remaining animals in drug week 12 correlated with the increase in dosage from 2.0 to 2.5 mg/kg/day in drug weeks 11 and 12. The tremors in all the affected animals persisted intermittently until the time of sacrifice. High-dose animals Nos. 82-7691 F, 82-7692 M, and 82-7742 M, which exhibited tremors, were sacrificed in a moribund condition on days 80, 299, and 315 of the study. The only other animal with tremors No. 82-7741 F, was sacrificed at the interim necropsy in scheduled sacrifice on day 371 of the study."

The days on study of the control animals which were unscheduled deaths as follows: Control I: 82-7161 F (360 days), 82-7177 F (234 days), 82-7193 F (290 days), 82-7128 M (345 days), 82-7150 M (154 days), 82-7154 M (311 days); Control II: 82-7263 F (226 days), 82-7264 M (336 days), 82-7346 M (351 days). In comparison to controls, the unscheduled deaths of animals in the high-dose group occurred more frequently at an earlier time. This may be due to the compound-related tremors during the early stages of the study.

The days on s treated animals which were unscheduled deaths is as : low-dose: 82-7453 F (310 days), 82-7487 F (34 days), 82-7402 (256 days), 82-7410 (343 days); mid-dose: 82-7565 F (331 days), 82-7540 (348 days), 82-7592 (46 days); high-dose: 82-7673 F (183 days), 82-7691 F (80 days), 82-7650 M (350 days), 82-7652 M (263 days), 82-766 M (32 days), 82-7670 M (172 days), 82-7692 M (299 days), 82-7742 M (315 days).

Average body weight of male and female treated rats in all groups were increased in comparison to controls during the interim period. After 52 weeks of treatment, body weight gains in each of the treated groups of males averaged about 10 percent above the combined controls; the average body weight gain of high-dose males being slightly less than the average body weight gain of mid- and high-dose males during the interim period. The average weight change for males in Control I, Control II, low-, mid-, and high-dose groups was 553, 556, 617, 608, and 602 g, respectively.

After 52 weeks of treatment, body weight gains in each of the treated female groups averaged an increase of about 21, 10, and 7 percent for the low-, mid-, and high-dose respectively, above the combined controls. The average weight for females in Control I, Control II, low-, mid-, and high-dose groups was 309, 310, 391, 342, and 333 g, respectively.

This increase in body weight gain is considered to be a secondary effect of the antiparastic activity of MK-0936

and has been observed in other rat studies (TT #82-705-0 and 829010). Food consumption (g/kg) in the treated animals of both sexes was comparable to control values throughout the study.

Mean compound intake values in female varied between 0.6 through 0.9 mg/kg/day for low-dose, 1.2 through 1.7 mg/kg/day for mid-dose and 1.6 through 2.6 mg/kg/day for high-dose groups.

In males, mean compound intake values varied between 0.6 through 0.8 mg/kg/day for low-dose, 1.1 through 1.6 mg/kg/day for mid-dose, and 1.4 through 2.8 mg/kg/day for high-dose groups.

Ophthalmic examination data were not provided for evaluation. The report states that "ocular abnormalities noted in the high-dose and control animals in drug weeks 26 and 52 (males) and 53 (females) were of the type commonly observed in laboratory rats. There was no evidence of any compound-related ocular abnormality."

With respect to hematological values, male rat 82-7734 of the high-dose group had an erythrocyte value of 3.84 million/mm^3 at week 38. This animal showed other hematological signs of anemia. The erythrocyte assay was repeated at week 40 and was 6.90 million/mm^3. At week 51, this animal had a 7.76 million/mm^3 value for erythrocytes. This transient effect was not considered compound-related.

There were no compound-related hematological findings during the interim period.

There were no compound-related hematological findings during the interim period.

There were no compound-related serum biochemical findings during the interim period.

Urinalyses data (tables A-101 to A-123) were not submitted for evaluation. The report states that "no treatment-related effects were observed."

B. Postmortem Phase

There was no postmortem report (pages 925 through 1001 of the report were apparently inadvertently omitted). Only organ weights and histological examination of tissues were submitted.

For the interim report, analyses of organ weight tables indicates that absolute organ weights of individual

female animals of the Control I, Control II, low-, and mid-dose groups were not submitted. The following number of animals had organ weights presented in the report: females: Control I (15), Control II (15), low-dose (14), mid-dose (15), high-dose (15); males: Control I (15), Control II (14), low-dose (15) mid-dose (14), and high-dose (14).

However, the number of animals with histomorphology for the interim report were as follows: females: Control I (15), Control II (14), low-dose (12), mid-dose (11), high-dose (15); males: Control I (15), Control II (8), low-dose (11), mid-dose (10), and high-dose (14). These discrepancies are required to be resolved.

Male and female organ weights expressed as a percent of body weight and percent brain weight did not show any compound-related effects.

There were no compound-related effects in the histomorphology of animals which were unscheduled deaths. There were no compound-related histomorphology findings in animals sacrificed at the interim period which were reported.

Conclusion: A NOEL cannot be established from the submitted data. There was no postmortem report. Only organ weights and histomorphological examination of the tissues were submitted. The postmortem report of the interim report needs to be submitted. There were compound-related increases in tremors in high-dose animals and a compound-related increase in unscheduled deaths at the high-dose. Average body weight gains of male and female rats of the treated groups were increased in comparison to controls. Food consumption in the treated animals of both sexes was comparable to control values throughout the study. Ophthalmic examination data were not provided for evaluation.

There were no compound-related effects in hematological or serum biochemical findings. Urinalyses data were not submitted for evaluation.

Analyses of organ weight tables indicates that absolute organ weights for individual female animals of Control I, Control II, low-, and mid-dose groups were not submitted. The following number of animals had organ weights presented in the report: females: Control I (15), Control II (15), low-dose (14), mid-dose (15), high-dose (15); males: Control I (15), Control II (14), low-dose (15), mid-dose (14), high-dose (14).

However, the number of animals with histomorphology for the interim report were as follows: females: Control I

(15), Control II (14), low-dose (12), mid-dose (11), high-dose (15); males: Control I (15), Control II (8), low-dose (11), mid-dose (10) and high-dose (14). These discrepancies are required to be resolved. There were no compound-related effects in histomorphology of animals which were unscheduled deaths. There were no compound-related histomorphological findings in animals sacrificed at the interim period which were reported.

Classification: Supplementary (pending additional information cited below):

(1) In the interim report of the chronic rat study, there was no postmortem report. Only organ weights and histomorphological examination of the tissues were submitted. The postmortem report of the interim report needs to be submitted.

(2) For the interim report, the following tables were not submitted: Urinalyses, tables A-101 to A-123. These tables are required to be submitted.

(3) Analyses of organ weight tables indicate that absolute organ weights of individual female animals of the Control I, Control II, low-, and mid-dose groups were not submitted. These data are required to be submitted.

(4) The following number of animals had organ weights presented in the report: females, Control I (15), Control II (15), low-dose (14), mid-dose (15), high-dose (15); males, Control I (15), Control II (14), low-dose (15), mid-dose (14), and high-dose (14). However, the number of animals with histomorphology for the interim report were as follows: females, Control I (15), Control II (14), low-dose (12), mid-dose (11), high-dose (15); males, Control I (15), Control II (8), low-dose (11), mid-dose (10), and high-dose (14). These descrepancies are required to be resolved.

(5) Ophthamological examinations for the interim report are required.

For the final reports of the rat and mouse oncogenicity studies, the following are required.

(1) TB requires a listing of all gross necropsy observations and palpable masses and corresponding microscopic findings for each animal. The day of death of each animal should also be included.

(2) TB requires reformatted pathology reports of histopathology incidence tables and summary incidence tables

for both the final reports of the rat and mouse oncogenicity studies. Sample sheets of these reformatted tables are included.

R:90998:Dykstra:C.Disk:KENCO:1/6/86:TAR:VO:EK
R:91540:Dykstra:C.Disk:KENCO:3/16/87:de:VO:EK
R:91530:Dykstra:C.Disk:KENCO:3/23/87:de:lf:de:EK:kim:VO:kim
R:92177:Dykstra:C.Disk:KENCO:4/9/87:EK

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005850

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

March 27, 1987

SUBJECT: Avermectin B_1, Dermal Absorption

TO: Edwin Budd, Head
Review Section II
Toxicology Branch

FROM: Robert P. Zendzian PhD
Pharmacologist
Mission Support Staff
Toxicology Branch
HED (TS-769)

Based on the data submitted by the Registrant, Merk, one may reasonably conclude that the maximum dermal absorption of Avermection B_1 is one percent of the applied dose.

A meeting was held in Dr. Farber's office on March 27, 1987 at 9:00 A.M. with representatives of Mecck Sharp & Dohme concerning the dermal absorption of Avermectin B_1. The Registrant presented information on the dermal absorption, physical properties, metabolism and relative acute oral/dermal toxicity of Avermection B_1 (copy attached). The Registrant concluded that this information justified accepting a value of one percent as the maximum of Avermectin B_1. I agree with this conclusion.

Data Evalaution Report

005850

Compound Avermectin B_1a

Citation
Dermal peneration of Avermectin B_1a in the monkey, P.J. Wislocki and A.Y.H. Lu, Merck Sharp & Dohme Research Laboratories, PS#1. June 2 1986. Accession # 265590.

Reviewed by Robert P. Zendzian PhD 5/1/86
Pharmacologist

Core Classification Supplimentary

Conclusion Because of intrinsic uncertanties in this experimental design, the upper limits for dermal absorption of Avermectin B_1a should be used for regulatory purposes. These are: 6ug EC, 1hr 10.52 %, 10hr 14.44&; 300ug technical suspension 1hr 18.95%, 10hr 24.83% and 300ug EC, 1hr 3.30%, 10hr 4.26%

Materials

^3H-Avermectin B_1a 1.65 mCi/mg & 34 uCi/mg, from the radiosynthesis group at Merck.

Four mature, juvenile, male rhesus monkeys from Charles River Research Primates

Experimental Design

Aminals were dosed with test compound according to the following dose regimen in the order given. The high dose was chosen to duplicate exposure to the emulsifiable concentrate and the low dose, EC diluted in water, to the field use concentration. The technical suspension was to simulate field worker exposure to the dried material from the plant surface. The intravenous doses were given to 'calibrate' the excretion phase from the monkey.

Route	Dose microgram	Exposure Duration (hr)
iv	6	N/A
	300	N/A
Dermal	6 EC*	1
	6 EC	10
	300**	1
	300**	10
	300 EC	1
	300 EC	10

* EC emulsifiable concentrate
** technical suspension

Monkeys were fasted 18 hours before treatment and 8 or 10 hours after. Animals were immobilized with ketamine HCl, the left arm clipped and an area (6 cm^2, 2 X 3 cm) marked as the application area. Animals were chaired for 10 days for collection of urine and feces. The i.v. dose was administered in 1 ml DMSO. Dermal doses were applied under immobilization and the application area dried before rechairing. Blood samples were taken a 5, 15 and 30 min, 1, 2, 4, 8, and 24 hr and at 24 hour intervals thereafter until the monkeys were removed from the chairs. The 5 minute sample was omitted for the dermal doses and a 10 hour sample added for the ten hour dermal exposure.

At the end of the exposure period, the application site was washed with soapy water, rinsed and dried. The area was then wiped with an acetone wetted pad. Wash and rinse solutions were analysed for radioactivity. For the 6 ug EC 1hr, 6 ug EC 10-hr and 300 ug 1-hr doses, the application area was wiped with an acetone wetted pad ten days after treatment. Since this later wash produced only minimal radioactivity, it was not continued.

Results

The results of this study are summerized in the table on the following page. The basic data are from table 4 of the report.

Discussion

Dermal absorption studies are performed in the monkey because 'the skin of this primate is similar to that of man'. However, the use of this large, valuable animal produces certian restrictions in the experimental design which limit the sensitivity of the results. Also, since all doses are tested with the same four animals, the total number of dose regimens which can be tested is limited.

A dose of pesticide applied dermally can be expressed as four parts at the end of the application period; the part which can be washed off the skin, the part which is on/or in the skin (and potentially available for absorption), the part retained in the animal and the part excreted. Absorption can be calculated in two ways; 1) by subtracting the part washed off the skin from the dose or 2) by adding the parts on/in the skin, in the animal and excreted. The first calculation gives an upper limit to the absorption since the washing procedure is more likely to result in loss of material. The second calculation gives a lower limit to absorption and, if the material on/in the skin if proportionately large, indicates the potential for additional absortion following washing.

Table. Summary of Avermectin B_{1a} dermal absorption in the Monkey. Values are means of four animals.

Treatment (applied to 6 cm^2 shaved skin	% of dose recovered from skin	% of dose excreted in feces	% of dose excreted in urine	% of dose absorbed			% of dose missing (dose less % washed off & % excreted)
				dose applied less % dose recovered from skin	total of dose excreted in feces and urine	total of dose excreted in feces and urine corrected[a]	
6ug iv		92.95	2.34	N/A	95.29	N/A	N/A
300ug iv		93.73	3.29	N/A	97.02	N/A	N/A
6ug EC 1 hr diluted	89.48	0.17	0.03	10.52	0.20	0.31	10.33
6ug EC 10hr diluted	85.56	0.42	0.05	14.44	0.47	0.49	13.97
300ug 1hr technical suspension	81.06	0.09	0.06	18.95	0.15	0.15	18.79
300ug 10hr technical suspension	75.17	0.24	0.01	24.83	0.25	0.26	24.58
300ug EC 1hr	96.70	0.19	0.03	3.30	0.22	0.23	3.08
300ug EC 10hr	95.74	0.50	ND	4.26	0.50	0.52	3.75

a. corrected from excretion data of iv doses.
ND. none detected

With the monkey, which is to valuable to sacrifice, it is not possible to determine the amount of compound on/in the skin and in the body. This experimental design attempts to compensate for this by washing the application site with acetone at 10 days after dosing, collecting excreta for 10 days after dosing and by giving an intravenous dose of the test compound. Washing the site attempts to detects any additional material available due to the process of desquamination. Collecting excreta for 10 days attempts to cover the entire excretion of the test compound. The intravenous dose is a kinetic study which attempts to provide a correction factor for material retained in the body and to provide data on plasma compartment distribution of the test compound which omits the skin from the process.

The intravenous doses used in this experiment (and in this experimental design in general) are incorrect in that the dose applied is used and it is administered as a single, pulse dose. The intravenous dose used should approximate the quantity absorbed and not the quantity applied in order to produce the kinetics of distribution and excretion of that latter quantity. Whether that dose should approximate the absorption calculated from the quantity washed off the site or from the quantity excreted depends on the differences of these absorption values and must be justified for each particular compound.

The rate of administration of the intravenous dose should approximate the rate at which the test compound enters the plasma compartment through the skin. Absorption from the skin increases with time to a maximum rate which can continue, essentially linear, until it is washed off the skin or the rate can fall off with time if the quantity of test material on the skin is sufficiently depleted by absorption. Whether one should administer the intravenous dose as a constant infusion over a period equal to the exposure period or attempt to approximate the plasma curve from the dermal absorption is a matter to be determined expermentally.

Because of the uncertanties of this expermental design, the upper limits of dermal absorption should be used for regulatory purposes.

The protocol for this study was submitted by the Registrant and reviewed by the Agency (Zendzian 1985). The reviewer concluded, "In all other aspects the proposed study appears to be capable of generating usefull information." Information gained since that review has shown the problems associated with this protocol. For the majority of compounds the only usable data produced by this experimental design will be an upper limit of dermal absorption.

The Agency has available a protocol for studying dermal absorption of a pesticide in the rat. This protocol does not suffer from the deficiencies of the monkey protocol and properly performed will produce dermal absorption data which more closely approaches the 'true' dermal absorption.

Reference

Memo Zendzian to La Rocca; Avermectin, Protocol for Dermal Absorption in the Monkey, Feb 15, 1985

SAMPLE SHEET

EVERY PATHOLOGY REPORT SHOULD HAVE:
SUMMARY INCIDENCE TABLE

male Mice

	Group 1			Group 5			Group 6			Group 7		
	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total
NG (NO. EXAMINED)	(43)	(7)	(50)	(42)	(8)	(50)	(38)	(12)	(50)	(39)	(11)	(50)
Alveolar/Bronchiolar Carcinoma	2		2	2		2	2		2	3		3
Malignant Lymphoma					1	1		4	4		1	1
Malignant Lymphoma, Undifferentiated		2	2				1		1		1	1
Alveolar/Bronchiolar Adenoma	3		3	3		3	5	2	7	4		4
Carcinoma, Metastatic	1	1	2		1	1		2	2			
Granulocytic Leukemia					1	1						
Sarcoma, Metastatic												
Multifocal Pleuritis							1		1	3		3
Multifocal Pneumonitis	5		5	2		2	4		4	3		3
Alveolar Macrophages, Pigmented	7		7	4		4				1	1	2
Focal Alveolar/Bronchiolar Hyperplasia	2		2	2		2	2		2	1		1
Congestion	2	2	4	4	5	9	3	5	8	3	8	11
Focal Hemorrhage				2		2	1		1	1		1
Alveolar Macrophages	2		2	2		2	2		2	1		1
Foci of Foamy Macrophages	4		4	3		3				2		2
Leukocytosis				1	2	3					3	3

SAMPLE SHEET

EVERY PATHOLOGY REPORT SHOULD HAVE INDIVIDUAL:
HISTOPATHOLOGY INCIDENCE TABLE

005850

Group 1

Male Mice
Scheduled Sacrifices

ANIMAL NUMBER	16845 6	16845 7	16845 8	16845 9	16846 0	16846 1	16846 2	16846 3	16846 4	16846 5	16846 6	16846 7	16846 8	16846 9	16847 0	16847 1	16847 2	16847 3	16847 4
LUNG		X				X	X				X			X	X		X	X	X
Alveolar/Bronchiolar Carcinoma																			
Malignant Lymphoma																			
Malignant Lymphoma, Undifferentiated																			
Alveolar/Bronchiolar Adenoma								P		P									
Carcinoma, Metastatic																			
Granulocytic Leukemia																			
Sarcoma, Metastatic					P														
							-												
Multifocal Pleuritis																			
Multifocal Pneumonitis			2																
Alveolar Macrophages, Pigmented					.											1			
Focal Alveolar/Bronchiolar Hyperplasia																			
Congestion																			
Focal Hemorrhage									3										
Alveolar Macrophages																			
Foci of Foamy Macrophages																			
Leukocytosis																			
Peribronchial/Vascular Mononuclear Cells	1		1	1								2	1			1			
Alveolar Proteinosis																			
Multifocal Alveolar-Bronchiolitis	1															1			

Key: P = Present M = No Section A = Autolysed I = Not Examined

ToR Review 005850

Page _____ is not included in this copy.

Pages 60 through 64 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
